Official Title: A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) (MURANO)

NCT Number: **NCT02005471**

Document Dates: Protocol Amendment/Version 1: 07-Aug-13
Protocol Amendment/Version 7: 21-Nov-16

PROTOCOL

TITLE:	**A MULTICENTER, PHASE III, OPEN-LABEL, RANDOMIZED STUDY IN RELAPSED/REFRACTORY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TO EVALUATE THE BENEFIT OF GDC-0199 (ABT-199) PLUS RITUXIMAB COMPARED WITH BENDAMUSTINE PLUS RITUXIMAB**
PROTOCOL NUMBER:	GO28667
VERSION NUMBER:	1
EUDRACT NUMBER:	2013-002110-12
IND NUMBER:	110159
TEST PRODUCT:	GDC-0199 (ABT-199) (RO5537382)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd and AbbVie Inc will act as co-sponsors of this trial globally*
DATE FINAL:	See electronic date stamp below

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	07-Aug-2013 23:18:23

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TABLE OF CONTENTS

PROTOCOL ACCEPTANCE FORM 9

PROTOCOL SYNOPSIS 10

1. BACKGROUND 28
   - 1.1 Background on Chronic Lymphocytic Leukemia 28
   - 1.2 Background on GDC-0199 28
   - 1.2.1 Bcl-2 Protein Family 28
   - 1.2.2 GDC-0199 29
   - 1.2.2.1 GDC-0199 Nonclinical Activity and Pharmacokinetic Profile 29
   - 1.2.2.2 GDC-0199 Nonclinical Toxicology 30
   - 1.2.2.3 GDC-0199 Clinical Experience 31
   - 1.2.2.4 Clinical Pharmacokinetics and Pharmacodynamics 36
   - 1.3 Study Rationale and Benefit–Risk Assessment 37

2. OBJECTIVES 39
   - 2.1 Efficacy Objectives 39
   - 2.2 Safety Objectives 40
   - 2.3 Pharmacodynamic Objectives 40
   - 2.4 Pharmacokinetic Objectives 40
   - 2.5 Patient-Reported Outcome Objectives 40
   - 2.6 Health Economic Objectives 40
   - 2.7 Exploratory Objectives 41

3. STUDY DESIGN 41
   - 3.1 Description of Study 41
   - 3.1.1 Independent Review Committee 43
   - 3.1.2 Data Monitoring Committee 43
   - 3.2 End of Study 44
   - 3.3 Rationale for Study Design 44
   - 3.3.1 Rationale for Combination Therapy (Experimental Group) 44

3.3.1.1 Rationale for GDC-0199 Dosage 44
3.3.1.2 Rationale for Rituximab Dosage 45
3.3.1.3 Rationale for Duration of Therapy 45
3.3.2 Rationale for Control Group 45
3.3.2.1 Rationale for BR Dosage 46
3.3.3 Rationale for Patient Population 46
3.3.4 Rationale for Including Patients with 17p Deletion 48
3.3.5 Rationale for Biomarker Assessments 48
3.3.6 Rationale for Patient-Reported Outcome Assessments 49
3.4 Outcome Measures 49
3.4.1 Efficacy Outcome Measures 49
3.4.1.1 Primary Efficacy Outcome Measure 49
3.4.1.2 Secondary Efficacy Outcome Measures 49
3.4.2 Safety Outcome Measures 50
3.4.3 Pharmacodynamic Outcome Measures 50
3.4.4 Pharmacokinetic Outcome Measures 50
3.4.5 Patient-Reported Outcome Measures 51
3.4.6 Health Economic Outcome Measures 51
3.4.7 Exploratory Outcome Measures 51

4. MATERIALS AND METHODS 51
4.1 Patients 51
4.1.1 Inclusion Criteria 51
4.1.2 Exclusion Criteria 53
4.2 Method of Treatment Assignment and Blinding 55
4.3 Study Treatment 55
4.3.1 Formulation, Packaging, and Handling 55
4.3.1.1 GDC-0199 56
4.3.1.2 Rituximab 56
4.3.1.3 Bendamustine 56
4.3.2 Dosage, Administration, and Compliance 57
4.3.2.1 GDC-0199 57
4.3.2.2 Rituximab 59

4.3.2.3 Bendamustine ... 61
4.3.3 Investigational Medicinal Product Accountability ... 62
4.3.4 Post-Trial Access to GDC-0199 ... 62
4.4 Concomitant Therapy and Food ... 63
4.4.1 Permitted Therapy ... 63
4.4.1.1 Premedication before Rituximab ... 63
4.4.1.2 Prophylaxis and Management of Tumor Lysis Syndrome ... 64
4.4.1.3 Prophylaxis for Infections ... 68
4.4.2 Prohibited Therapy ... 68
4.4.3 Prohibited Food ... 70
4.5 Study Assessments ... 70
4.5.1 Description of Study Assessments ... 70
4.5.1.1 Medical History and Demographic Data ... 70
4.5.1.2 Physical Examinations ... 70
4.5.1.3 Vital Signs and ECOG Performance Status ... 71
4.5.1.4 Electrocardiogram ... 71
4.5.1.5 Assessment of Left Ventricular Ejection Fraction ... 71
4.5.1.6 Tumor and Response Evaluations ... 71
4.5.1.7 Laboratory Assessments ... 73
4.5.1.8 Patient-Reported Outcomes ... 74
4.5.1.9 Samples for Roche Clinical Repository ... 76
4.5.2 Timing of Study Assessments ... 78
4.5.2.1 Screening and Pretreatment Assessments ... 78
4.5.2.2 Assessments during Treatment ... 79
4.5.2.3 Assessments at End of Treatment/Early Termination Visit ... 79
4.5.2.4 Follow-Up Assessments ... 79
4.5.2.5 Assessments at Unplanned Visits ... 79
4.6 Patient, Study, and Site Discontinuation ... 80
4.6.1 Patient Discontinuation ... 80
4.6.1.1 Discontinuation from Study Drug/Treatment ... 80
4.6.1.2 Withdrawal from Study ... 81
4.6.2 Study and Site Discontinuation ... 81

5. ASSESSMENT OF SAFETY 81
5.1 Safety Plan 81
5.1.1 Risks Associated with GDC-0199 81
5.1.2 Risks Associated with Rituximab Therapy 83
5.1.3 Risks Associated with Bendamustine 85
5.1.4 Risks Associated with GDC-0199 and Rituximab Combination Therapy 86
5.1.5 Management of Specific Adverse Events 87
5.2 Safety Parameters and Definitions 92
5.2.1 Adverse Events 93
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 93
5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 94
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 94
5.3.1 Adverse Event Reporting Period 94
5.3.2 Eliciting Adverse Event Information 95
5.3.3 Assessment of Severity of Adverse Events 95
5.3.4 Assessment of Causality of Adverse Events 96
5.3.5 Procedures for Recording Adverse Events 96
5.3.5.1 Diagnosis versus Signs and Symptoms 96
5.3.5.2 Adverse Events Occurring Secondary to Other Events 97
5.3.5.3 Persistent or Recurrent Adverse Events 97
5.3.5.4 Abnormal Laboratory Values 97
5.3.5.5 Abnormal Vital Sign Values 98
5.3.5.6 Abnormal Liver Function Tests 99
5.3.5.7 Deaths 99
5.3.5.8 Preexisting Medical Conditions 100
5.3.5.9 Lack of Efficacy or Worsening of CLL 100
5.3.5.10 Hospitalization or Prolonged Hospitalization 100
5.3.5.11 Overdoses 101
5.3.5.12 Patient-Reported Outcome Data 101

5.4 Immediate Reporting Requirements from Investigator to Sponsor ... 101
5.4.1 Emergency Medical Contacts ... 102
5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest ... 102
5.4.3 Reporting Requirements for Pregnancies ... 103
5.4.3.1 Pregnancies in Female Patients ... 103
5.4.3.2 Pregnancies in Female Partners of Male Patients ... 103
5.4.3.3 Abortions ... 104
5.4.3.4 Congenital Anomalies/Birth Defects ... 104
5.5 Follow-Up of Patients after Adverse Events ... 104
5.5.1 Investigator Follow-Up ... 104
5.5.2 Sponsor Follow-Up ... 104
5.6 Post-Study Adverse Events ... 104
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees ... 105

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN ... 105
6.1 Determination of Sample Size ... 106
6.2 Summaries of Conduct of Study ... 106
6.3 Summaries of Treatment Group Comparability ... 106
6.4 Efficacy Analyses ... 106
6.4.1 Primary Efficacy Endpoint ... 107
6.4.2 Secondary Efficacy Endpoints ... 107
6.5 Safety Analyses ... 109
6.6 Pharmacodynamic Analyses ... 109
6.7 Pharmacokinetic Analyses ... 110
6.8 Patient-Reported Outcome Analyses ... 110
6.9 Health Economic Analysis ... 111
6.10 Exploratory Analyses ... 111
6.11 Interim Analyses ... 111

7. DATA COLLECTION AND MANAGEMENT ... 111
7.1 Data Quality Assurance ... 111

7.2 Electronic Case Report Forms 112
7.3 Electronic Patient-Reported Outcome Data 113
7.4 Source Data Documentation 113
7.5 Use of Computerized Systems 113
7.6 Retention of Records 114

8. ETHICAL CONSIDERATIONS 114
8.1 Compliance with Laws and Regulations 114
8.2 Informed Consent 114
8.3 Institutional Review Board or Ethics Committee 115
8.4 Confidentiality 116
8.5 Financial Disclosure 116

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 116
9.1 Study Documentation 116
9.2 Site Inspections 117
9.3 Administrative Structure 117
9.4 Publication of Data and Protection of Trade Secrets 117
9.5 Protocol Amendments 118

10. REFERENCES 119

LIST OF TABLES

Table 1 Administration of First and Subsequent Infusions of Rituximab 61
Table 2 Dose Modifications for GDC-0199+Rituximab – Hematologic Toxicity 87
Table 3 Dose Modifications for GDC-0199+Rituximab – Non-Hematologic Toxicity 89
Table 4 GDC-0199 Dose Reduction 90
Table 5 Bendamustine Dose Reduction 91
Table 6 Dose Modification Guidelines for Bendamustine 92
Table 7 Adverse Event Severity Grading Scale 95

LIST OF FIGURES

Figure 1 Study M12-175: Preliminary Mean (+ SD) GDC-0199 Plasma Concentration–Time Profiles Following Oral Administration of GDC-0199 (ABT-199) in Patients with CLL/SLL (Log-Linear Scale) 36
Figure 2 Study Schema 42
Figure 3 Initial Dose Increase during GDC-0199 Ramp-Up Period 58
Figure 4 GDC-0199 Dose Ramp-Up Period 58

LIST OF APPENDICES

Appendix 1 Schedule of Assessments 124
Appendix 2 Schedule of Pharmacokinetic Assessments 141
Appendix 3 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) 142
Appendix 4 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-CLL16) 145
Appendix 5 M. D. Anderson Symptom Inventory (MDASI) Questionnaire 146
Appendix 6 EQ-5D (U.S. Version) 148
Appendix 7 ECOG Performance Status Scale 150
Appendix 8 Treatment Options for CLL (Adapted from NCCN Version 3.2012 and 2011 ESMO Clinical Practice Guidelines) 151
Appendix 9 Sample List of Excluded and Cautionary Medications 154
Appendix 10 Cairo – Bishop Definition and Grading of Tumor Lysis Syndrome 156
Appendix 11 Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia 157
Appendix 12 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome 160

PROTOCOL ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd and AbbVie Inc will act as co-sponsors of this trial globally*

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, PHASE III, OPEN-LABEL, RANDOMIZED STUDY IN RELAPSED/REFRACTORY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TO EVALUATE THE BENEFIT OF GDC-0199 (ABT-199) PLUS RITUXIMAB COMPARED WITH BENDAMUSTINE PLUS RITUXIMAB**
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EUDRACT NUMBER:	2013-002110-12
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TEST PRODUCT:	GDC-0199 (ABT-199) (RO5537382)
PHASE:	III
INDICATION:	Chronic Lymphocytic Leukemia
SPONSOR:	F. Hoffmann-La Roche Ltd and AbbVie Inc will act as co-sponsors of this trial globally*

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Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of GDC-0199 and rituximab (GDC-0199+R) compared with bendamustine and rituximab (BR) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) as measured by investigator-assessed progression-free survival (PFS).

The secondary efficacy objectives for this study are as follows:

- To analyze Independent Review Committee (IRC)-assessed PFS in the subset of CLL patients with 17p deletion identified by fluorescence in situ hybridization (FISH) testing performed at a central laboratory.
- To evaluate PFS as assessed by an IRC.
- To analyze investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by fluorescence in situ hybridization (FISH) testing performed at a central laboratory.
- To evaluate rates of overall response (OR; defined as complete response [CR], CRi [complete response with incomplete marrow recovery], and PR [partial response]), PR, and CR and CRi at 12 weeks after Day 1 of the last cycle of multi-agent therapy, as assessed by the investigator.
- To evaluate OR, PR, CR, and CRi rates 12 weeks after Day 1 of the last cycle of multi-agent therapy, as determined by the IRC.
- To evaluate PFS as assessed by the investigator and by the IRC.
- To evaluate overall survival (OS).

- To evaluate duration of response (DOR) for patients with a best overall response of CR, CRi, or PR.
- To evaluate time to next anti-CLL treatment (TTNT).
- To evaluate the proportion of patients with minimal residual disease (MRD)-negativity at the disease response assessment time points.

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of GDC-0199 and rituximab compared with BR in patients with relapsed or refractory CLL, focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities.

Pharmacodynamic Objectives

The pharmacodynamic (PD) objective for this study is as follows:

- To assess changes in lymphocyte subset counts during the study (eg, T and B cells).

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of GDC-0199 in patients with relapsed or refractory CLL.

Patient-Reported Outcome Objectives

The patient-reported outcome (PRO) objectives for this study are as follows:

- To compare treatment-related symptoms following treatment with GDC-0199 and rituximab compared with BR in patients with relapsed or refractory CLL, as measured by M. D. Anderson Symptom Inventory (MDASI) and European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and associated CLL module (QLQ-CLL16).
- To evaluate changes from baseline CLL symptoms scores using MDASI and EORTC QLQ-C30 and QLQ-CLL16 questionnaires.
- To evaluate time to disease-related symptom progression using EORTC QLQ-CLL16 health-related quality of life (HRQoL) using global health status/quality of life (QoL) and other functional subscales of QLQ-C30.
- To assess interference of treatment and disease-related symptoms on QoL using the MDASI questionnaire.

Health Economic Objectives

The health economic objective for this study is as follows:

- To compare the health economic effects of GDC-0199 in combination with rituximab versus BR in patients with relapsed or refractory CLL as measured by the EuroQol 5 Dimension (EQ-5D) questionnaire.

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the relationship between efficacy outcome and potential biomarkers, including Bcl-2 expression, for patients treated with GDC-0199 and rituximab compared with BR.
- To evaluate potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with GDC-0199 and rituximab or with BR.

Study Design

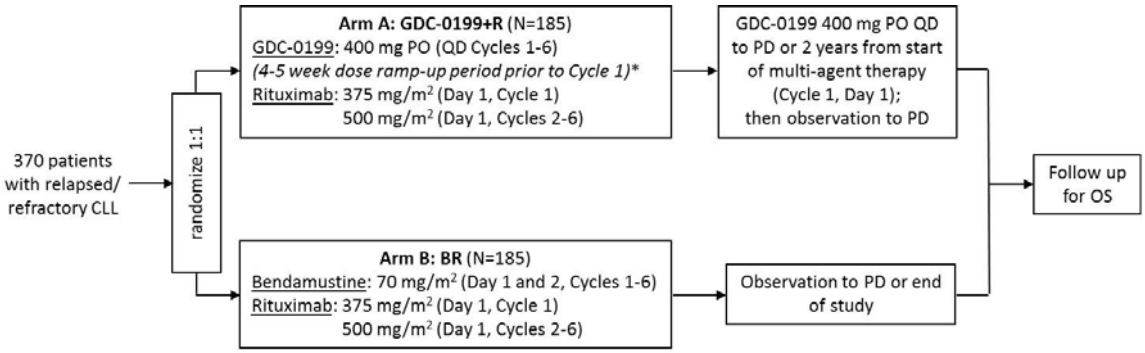
Description of Study

This is an open-label, international, multicenter, randomized, phase III study to investigate the efficacy and safety of GDC-0199 in combination with rituximab (GDC-0199+R) compared with bendamustine in combination with rituximab (BR) in patients with relapsed or refractory CLL.

Approximately 370 patients will be enrolled and randomized 1:1 to receive either GDC-0199+R (Arm A) or BR (Arm B). Randomization will be stratified according to the following factors:

- 17p deletion: yes or no
- risk status: high risk or low risk
- geographic region: U.S./Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America.

Study Schema



Patients randomized to Arm A (GDC-199+R) will have a 4 – 5 week GDC-0199 dose ramp-up period to reach the target dose of 400 mg daily. Following the GDC-0199 ramp-up period, patients will receive 6 cycles of rituximab consisting of a single infusion on the first day of each 28-day cycle. Patients will continue to take their daily dose of GDC-0199 during the rituximab cycles. Patients who have not progressed following the completion of the 6 cycles will continue to receive GDC-0199 until disease progression or for a maximum of 2 years from Cycle 1 Day 1.

Patients randomized to Arm B (BR) will receive 6 cycles of BR consisting of a single infusion of rituximab on Day 1 and bendamustine infusions on Days 1 and 2 of each 28-day cycle. After completion of the 6 cycles, patients will continue to be followed up until progression or study end.

All patients will be assessed for response to treatment by the investigator using standard clinical and laboratory examinations and CT scans according to iwCLL guidelines (Hallek et al. 2008) at screening and at the following time points (selected to mirror those used in current phase III CLL protocols [CLL10, CLL11]):

- interim assessment (within 14 days of Cycle 4, Day 1)
- at completion of multi-agent therapy (4 weeks ± 7 days after Day 1 of the last cycle of rituximab (Arm A) or BR (Arm B), clinical assessment only)
- 8 – 12 weeks after multi-agent therapy (defined as 8 – 12 weeks after Day 1 of Cycle 6 or 8 – 12 weeks after Day 1 of the last cycle for early termination).

Following 6 cycles of multi-agent therapy, patients in both arms who have not progressed will be followed clinically every 3 months through Year 3 from initiation of multi-agent therapy (Cycle 1, Day 1). Patients will then be followed every 6 months until disease progression, study withdrawal, or end of study, whichever comes first. At each follow-up visit, patients will be assessed for response/progression by physical examination and laboratory tests. In addition, at any time during follow-up when clinical or laboratory findings suggest that the response may have improved from stable disease (SD) to PR, or from PR to CR, imaging should be performed to confirm the response. Imaging is not routinely required to determine PD, as objective

evidence of PD is most often documented by measurement of elevated peripheral CLL cells. However, when PD cannot be documented by increasing peripheral blood counts, imaging is required to document PD detected by physical examination or suspected based on symptoms.

After 5 years in the study or after disease progression (whichever comes first), patients will be followed annually for OS, PD, and new anti-CLL therapy until up to 3 years after the last patient is enrolled, withdrawal of consent, or the end of study, whichever comes first. Annual follow-up may be conducted by telephone contact.

Patients who discontinue all components of study therapy either prior to completion of planned therapy or prior to disease progression (eg, for toxicity) will continue to be followed for MRD levels, PD, and OS (regardless of whether they subsequently receive new anti-CLL therapy).

An independent review of the responses of all patients will also be conducted to confirm the primary PFS endpoint, including blinded review of clinical and laboratory findings as well as blinded radiology review of imaging assessments.

Number of Patients

Approximately 370 patients will be recruited from approximately 150 centers in up to 29 countries and randomly assigned in 1:1 ratio to receive either GDC-0199+R (Arm A) or BR (Arm B).

Target Population

The target population for this study is adult patients with relapsed or refractory CLL requiring treatment. Patients must meet the following criteria for study entry:

- Signed informed consent.
- Age $\geq$ 18 years.
- Diagnosis of CLL that meets published diagnostic criteria (Hallek et al. 2008). Patients must have peripheral blood B-lymphocyte counts which clonally express CD5, CD19/20, and CD23 and are either kappa or lambda light-chain-restricted. Pro-lymphocytes may comprise no more than 55% of total circulating lymphocytes. At initial diagnosis of CLL (ie, prior to front-line treatment), the peripheral lymphocyte count must have been $>$5000/mm^3. Patients must meet the following criteria for relapsed or refractory CLL (per the iwCLL guidelines [Hallek et al. 2008]):
  - Relapsed disease: a patient who previously achieved a CR or PR, but after a period of 6 months or more demonstrates evidence of progression;
  - Refractory disease: treatment failure or disease progression within 6 months of the last anti-leukemia therapy.
- Previously treated with at least one but not more than three lines of therapy (a line of therapy is defined as completing at least two cycles of treatment for a given line of therapy), including at least one prior standard chemotherapy-containing regimen according to current guidelines.
- For patients with 17p deletion, previously treated with at least one but not more than three lines of therapy, including at least one prior standard chemotherapy-containing regimen according to current guidelines OR at least one prior alemtuzumab-containing therapy.
- Patients previously treated with bendamustine only if their duration of response was $\geq$24 months.
- Patient requires treatment in the opinion of the investigator.
- Eastern Cooperative Oncology Group (ECOG) performance score of $\leq$1.
- Adequate BM function independent of growth factor or transfusion support, per local laboratory reference range at screening as follows:
  - platelet count $\geq$ 75 000/mm^3;
  - absolute neutrophil count (ANC) $\geq$1000/mm^3 unless cytopenia is clearly due to marrow involvement of CLL;
  - total hemoglobin $\geq$9 g/dL (without transfusion support within 2 weeks of screening);

- if any of the above-mentioned cytopenias are present, there should be no evidence of myelodysplastic syndrome (MDS) or hypoplastic BM.

- Adequate renal and hepatic function, per laboratory reference range at screening as follows:
  - Calculated creatinine clearance $\geq$ 50 mL/min using 24-hour creatinine clearance or modified Cockcroft – Gault equation (using ideal body mass [IBM] instead of mass):

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

    Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/L})}$$

    IBM should be used:
    IBM (kg) = [(height in cm – 154) × 0.9] + (50 if male, 45.5 if female)
  - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 3.0 × the upper limit of normal (ULN) of the institution's normal range;
  - bilirubin $\leq$ 1.5 × ULN. Patients with Gilbert's syndrome may have a bilirubin level > 1.5 × ULN, per discussion between the investigator and the Medical Monitor;
  - prothrombin time (or international normalized ratio) and partial thromboplastin time not to exceed 1.2 × the institution's normal range (patients with an elevated prothrombin time and known lupus anticoagulant may be eligible for participation after consulting the Medical Monitor).
- Female patients must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:
  - at screening, on a serum sample obtained within 14 days prior to initiation of study treatment, and
  - prior to dosing, on a urine sample obtained on Week 1 Day 1 if it has been > 7 days since obtaining the serum pregnancy test result.
- Female patients who are not surgically sterile or postmenopausal (for at least 1 year) must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after completing therapy with rituximab:
  - total abstinence from sexual intercourse;
  - a vasectomized partner;
  - hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) that started at least 3 months prior to study drug administration;
  - double-barrier method (condom + diaphragm or cervical cup with spermicidal contraceptive sponge, jellies, or cream).
- Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after completing therapy with rituximab:
  - a partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration;
  - total abstinence from sexual intercourse;
  - double-barrier method (condom + diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream).

Patients who meet any of the following criteria will be excluded from study entry:

- Transformation of CLL to aggressive NHL (eg, Richter's transformation, prolymphocytic leukemia, or DLBCL) or CNS involvement by CLL.
- Undergone an allogeneic stem cell transplant.

- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia.
- History of intolerance to prior bendamustine treatment (defined as toxicity requiring permanent discontinuation of bendamustine) or other contraindication to bendamustine treatment.
- History of severe (ie, requiring permanent discontinuation of prior rituximab therapy) prior allergic or anaphylactic reactions to rituximab.
- Known HIV-positivity.
- Positive hepatitis serology (serology testing required at screening), as follows:
  - Hepatitis B virus (HBV): Patients with positive serology for hepatitis B defined as positivity for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc).
  - Hepatitis C virus (HCV): Patients with positive hepatitis C serology unless HCV (RNA) is confirmed negative. Note that patients with HCV- or hepatitis C virus core antibody (HCVcAB)-positivity who have received recent IV IgG should be evaluated further for risk of viral reactivation and may be eligible for the study after discussion with the Medical Monitor.
- Requires the use of warfarin (due to potential drug – drug interactions that may potentially increase the exposure of warfarin). Patients may be eligible if able to be taken off warfarin and started on an alternative anticoagulant.
- Received an anti-CLL monoclonal antibody within 8 weeks prior to the first dose of study drug.
- Received any of the following agents within 14 days prior to the first dose of study drug, or has not recovered to less than Grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
  - any anti-cancer therapy including chemotherapy or radiotherapy and steroid therapy for anti-neoplastic intent;
  - investigational therapy, including targeted small-molecule agents.
- Received CYP3A4 inhibitors (such as fluconazole, ketoconazole, and clarithromycin) within 7 days prior to the first dose of GDC-0199.
- Received potent CYP3A4 inducers (such as rifampin, carbamazepine, phenytoin, St. John's Wort) within 7 days prior to the first dose of GDC-0199.
- History of prior GDC-0199 treatment.
- Consumed grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of GDC-0199.
- A cardiovascular disability status of New York Heart Association Class ≥ 3. Class 3 is defined as cardiac disease in which patients are comfortable at rest but marked limitation of physical activity due to fatigue, palpitations, dyspnea, or anginal pain.
- A significant history of renal, neurologic, psychiatric, endocrine, metabolic, immunologic, cardiovascular, or hepatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes.
- A female patient who is pregnant or breast-feeding.
- History of prior other malignancy that could affect compliance with the protocol or interpretation of results with the exception of the following:
  - curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study;
  - other cancers not specified above which have been curatively treated by surgery and/or radiation therapy from which patient is disease-free for ≥ 5 years without further treatment.
- Malabsorption syndrome or other condition that precludes enteral route of administration.
- Known allergy to both xanthine oxidase inhibitors and rasburicase.

- Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal).
- Vaccination with a live vaccine within 28 days prior to randomization.

Length of Study

The approximate length of the study will be 56 months, based on an enrolment period of 20 months and the end of study as defined below.

End of Study

The end of the study will be approximately 3 years after last patient is enrolled allowing for completion of the maximum duration of planned therapy (in the absence of disease progression) as well as at least one year of follow-up for all patients.

Efficacy Outcome Measures

Primary Efficacy Outcome Measures

- The primary efficacy outcome measure for this study is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse, determined using standard iwCLL guidelines (Hallek et al. 2008), or death from any cause, whichever comes first.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- IRC-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory.
- IRC-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse, or death from any cause.
- Investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory.
- Overall response (OR; defined as complete response [CR], complete response with incomplete marrow recovery [CRi], and partial response [PR]), PR, and CR/CRi rates at 12 weeks after Day 1 of the last cycle of multi-agent therapy, as assessed by the investigator. Disease response will be assessed according to the iwCLL guidelines (Hallek et al. 2008).
- OR, PR, CR, and CRi rates 12 weeks after Day 1 of the last cycle of multi-agent therapy, as assessed by the IRC.
- Investigator-assessed PFS and IRC-assessed PFS.
- Overall survival (OS), defined as the time from randomization to death from any cause.
- Duration of response (DOR), defined for patients with a best OR of CR, CRi, or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse, as assessed by the investigator, or death from any cause.
- Time to next anti-CLL treatment (TTNT), defined as the time from randomization to start of new non-protocol anti-CLL therapy or death from any cause.
- Proportion of patients with MRD-negativity at the disease response assessment time points as measured at a central laboratory on peripheral blood and/or BM samples.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs).
- Changes in clinical laboratory results (including hematology and chemistry) during and following administration of study treatment.

- Incidence of AEs of special interest:
  - Grade > 3 TLS and IRRs
- Measures of immune function, including serial immunoglobulin levels (IgG, IgM, IgA) following treatment with GDC-0199+R or BR.

Pharmacodynamic Outcome Measures

The pharmacodynamic outcome measure for this study is as follows:

- Serial assessment of B- and T-cell lymphocyte subsets by flow cytometry.

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Apparent clearance, apparent volume of distribution, and other appropriate PK parameters of GDC-0199 characterized using population PK techniques.

Patient-Reported Outcome Measures

The PRO outcome measures for this study are as follows:

- M. D. Anderson Symptom Inventory (MDASI)
- European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and associated CLL module (QLQ-CLL16).

Health Economic Outcome Measures

The health economic outcome measure for this study is as follows:

- The EuroQol 5-Dimension (EQ-5D) questionnaire.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Evaluation of the relationship between response and PFS and various potential biomarkers, including Bcl-2 expression, for patients treated with GDC-0199+R or BR.
- Assessment of potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with GDC-0199+R or BR.

Investigational Medicinal Products

Test Product

Arm A: GDC-0199 and Rituximab (GDC-0199+R)

- GDC-0199 tablets will be administered daily orally, starting with a test dose of 20 mg on Day 1 of the GDC-0199 dose ramp-up period, followed (if tolerated) by 50 mg daily from Day 2 to Day 7 followed by 100 mg daily from Day 8 to Day 14, followed by 200 mg daily from Day 15 to Day 21, followed by 400 mg daily from Day 22 to Day 28. There is a possibility that this dose ramp-up period may be one extra week longer to account for a possible continuation of the 20 mg test dose for 1 week prior to increasing the dose to 50 mg. GDC-0199 will then be self-administered at 400 mg per day for a maximum of 2 years from Cycle 1, Day 1 or until disease progression (whichever is earlier). Multi-agent therapy consisting of 6 cycles of rituximab and daily GDC-0199 dosing will start after completion of the GDC-0199 ramp-up period.
- Rituximab will be administered intravenously at a dose of 375 mg/m^2 on Day 1 of Cycle 1 followed by 500 mg/m^2 IV on Day 1 of Cycles 2 through 6.

Comparator

Arm B: Bendamustine and Rituximab (BR):

- Bendamustine will be administered at 70 mg/m^2 IV on Days 1 and 2 of Cycles 1 through 6.

- Rituximab will be administered at 375 mg/m^2 IV on Day 1 of Cycle 1 and 500 mg/m^2 IV on Day 1 of Cycles 2 through 6.

Non-Investigational Medicinal Products

Permitted Concomitant Therapy and Clinical Practice

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use for the duration of the study or at least one year after the last dose of rituximab, whichever is longer.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (eg, erythropoietin) if clinically indicated. G-CSF may be administered as primary prophylaxis in each cycle of therapy, as per the ASCO guidelines or each site's institutional standards.

Antiemetic therapy may be instituted for any patient if clinically indicated. Bendamustine has a moderate risk of emesis. It is recommended that bendamustine infusions be administered following premedication with a serotonin (5-HT3) antagonist (ie, dolasteron, ondansetron, etc.) or as per institutional practice.

Systemic steroid therapy will not be allowed either during or within 7 days prior to the first dose of study treatment with the exception of inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease (COPD), single infusions of hydrocortisone prior to rituximab infusions, topical steroids, or replacement corticosteroid therapy for an inherited or acquired deficiency.

Premedication before rituximab infusion:

- Oral acetaminophen/paracetamol ($650-1000$ mg) at least 30 min prior to the start of the first infusion (mandatory for all infusions)
- Antihistamine such as diphenhydramine ($25-50$ mg) approximately 30 min prior to the start of the first infusion for all subsequent infusions unless previous antibody infusions did not result in an IRR $>$ NCI CTCAE Grade 1 and there was no interruption to the infusion.
- A single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered with rituximab if this is the usual practice at the site.

Prophylaxis and Management of Tumor Lysis Syndrome (TLS)

Clinical data from CLL patients treated to date with GDC-0199 suggest that patients with baseline lymph nodes ≥ 5 cm diameter are at a greater risk for TLS than those with baseline lymph nodes less than 5 cm. In addition, the data showed that creatinine clearance of ≤ 80 mL/min at screening was a secondary risk factor for TLS. Based on the data review performed by the Sponsors, the following three risk categories for developing TLS were developed:

1. **Low-risk category**: the presence of all measurable lymph nodes with the largest diameter < 5 cm by radiographic assessment AND absolute lymphocyte counts $< 25 \times 10^9$/L.
2. **Medium-risk category**: the presence of all measurable lymph nodes with the largest diameter ≥ 5 cm and < 10 cm by radiologic assessment OR absolute lymphocyte count $\geq 25 \times 10^9$/L.
3. **High-risk category**: the presence of any lymph node with the largest diameter ≥ 10 cm by radiologic assessment OR the presence of BOTH an absolute lymphocyte count $\geq 25 \times 10^9$/L AND a measurable lymph node with the largest diameter ≥ 5 cm by radiologic assessment.

All patients enrolling in the study will be assessed at screening and categorized in a risk category as described above.

Initial Dosing

All patients, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to the initiation of the first dose of GDC-0199:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with GDC-0199 and rituximab is completed; rasburicase may be used at the investigator's discretion (0.2 mg/kg as an IV infusion over 30 minutes prior to the first dose of GDC-0199 and subsequently daily for up to 5 days).
- Oral hydration consisting of fluid intake of approximately 3 L/day starting at least 48 hours days prior to the start of treatment.
- Hospitalization for the first GDC-0199 dose of 20 and 50 mg beginning the evening prior to the dose of GDC-0199 and continuing for 24 hours after. Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of 150 to 200 cc/h or as clinically appropriate. Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities prior to the first dose of GDC-0199, or the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- **For patients at high risk for developing TLS**, rasburicase must be administered as prophylaxis at 0.2 mg/kg as an IV infusion over 30 minutes prior to the first dose of GDC-0199 and subsequently daily as needed for up to 5 days. For patients with a contraindication to rasburicase (ie, glucose-6-phosphate dehydrogenase (G6PD) deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in Section 4.5.1.7.

Serial vital signs and TLS laboratory samples will be drawn prior to the first dose of GDC-0199 and at 4, 6, 8, 10, 12, and 24 hours post-dose; additionally, hematology samples will be drawn at 8 and 24 hours post-dose. These samples are to be sent STAT to the laboratory, and the results must be reviewed promptly by the investigator or sub-investigator. Laboratory values obtained prior to the dose of GDC-0199 are to be used to determine whether a patient has developed changes related to TLS and as a baseline for evaluating changes in ALC. GDC-0199 cannot be administered on Day 2 of the GDC-0199 dose ramp-up period until the 24-hour post-dose laboratory values are reviewed.

Following the initial dosing, patients will be monitored to see if they meet any of the following conditions:

1. Evidence of one or more electrolyte abnormalities as defined by Cairo – Bishop criteria or clinical TLS.
2. For patients with a predose absolute lymphocyte count $\geq 5 \times 10^9$/L, a reduction in ALC from the predose value greater than 30%.

Patients with evidence of one or more laboratory abnormality as defined by Cairo – Bishop criteria or clinical TLS will have their dose of GDC-0199 held and will undergo aggressive management and further monitoring (as per the electrolyte management guideline with detailed intervention steps provided in Appendix 12 to aid in treatment and prevention of TLS) until their laboratory abnormality or clinical symptoms resolve. They will then complete one week with daily dosing of 20 mg GDC-0199. Following the week of 20 mg of GDC-0199 therapy, patients will receive TLS prophylaxis and hospitalization as described above and escalate to 50 mg of GDC-0199.

Patients with a pre-dose ALC $\geq 5 \times 10^9$/L who experience a reduction in ALC of greater than 30% from baseline (pre-dose) in the absence of electrolyte changes (evidence of one or more laboratory abnormalities as defined by Cairo – Bishop criteria or clinical TLS) will continue daily dosing with 20 mg of GDC-0199 for a week. Following the week of 20 mg of GDC-0199 therapy,

patients will receive TLS prophylaxis and hospitalization as described above and escalate to 50 mg of GDC-0199. During hospitalization, serial vital signs and TLS laboratory samples will be drawn prior to the dose of GDC-0199 and at 4, 6, 8, 10, 12, and 24 hours post-dose; additionally, hematology samples will be drawn at 8 and 24 hours post-dose.

If the laboratory results do not show evidence of one or more laboratory abnormality as defined by Cairo – Bishop criteria or clinical TLS or a reduction in ALC greater than 30% (for patients with a pre-dose ALC $\geq 5 \times 10^9$/L) during the initial 24 hours monitoring after the first 20 mg dose, patients will receive a 50 mg dose on Day 2 and have TLS laboratory samples and vital signs collected at 4, 6, 8, 10, 12, and 24 hours following the first dose of 50 mg; additionally, hematology samples will be drawn at 8 and 24 hours post-dose. The second 50 mg dose of GDC-0199 should not be administered until the Investigator or designee reviews the 24-hour laboratory results following the first 50 mg dose of GDC-0199. Patients may be discharged home if they are asymptomatic and the Investigator deems their condition to be stable.

Patients will also have TLS laboratory parameters and vital signs assessed at 48 hours and 72 hours after the first dose of GDC-0199; these laboratory tests may be performed as an outpatient, but results must be reviewed prior to the patient receiving the next scheduled daily dose of GDC-0199.

Subsequent Dose Increases during the GDC-0199 Ramp-Up Period

Low- and medium-risk patients are required to be hospitalized only for the initial dose of 20 and 50 mg of GDC-0199. Subsequent dose escalations do not require hospitalization but may be performed at the discretion of the investigator. Dose-escalation visits with hospitalization require collection of vital signs, TLS laboratory samples at pre-dose and 4, 8, 12, and 24 hours post-dose, and hematology samples at pre-dose and 8 and 24 hours post-dose. Dose-escalation visits without hospitalization require collection of serial vital signs and TLS laboratory and hematology samples at pre-dose and 8 and 24 hours post-dose.

All **high-risk patients** are required to be hospitalized for each dose escalation of GDC-0199 and must receive inpatient procedures (IV hydration, nephrology consult, and serial vital signs and laboratory monitoring) like the first dose. Dose-escalation visits with hospitalization require collection of vital signs, TLS laboratory samples at pre-dose and 4, 8, 12, and 24 hours post-dose, and hematology samples at pre-dose and 8 and 24 hours post-dose. If patients do not develop laboratory or clinical TLS 24 hours after a dose escalation, they can be discharged from the hospital if the investigator feels they are otherwise stable. TLS laboratory values and vital signs for the 24-hour post-dose time point must be reviewed promptly by the investigator or sub-investigator prior to the patient leaving the clinic or receiving any additional study drug.

Patients classified as high risk for developing TLS who presented at screening with BOTH an absolute lymphocyte count $\geq 25 \times 10^9$/L AND a measurable lymph node with the largest diameter ≥ 5 cm by radiologic assessment may have their TLS risk category reassessed. Prior to dose increases above 50 mg of GDC-199, patients may have a reassessment of their disease status based on their most recent ALC. Based on those results, one of the following two options may be implemented:

- If the patient's ALC decreases to $< 25 \times 10^9$/L, patients may be re-categorized as medium risk and follow the management guidelines for the medium-risk category for the subsequent increases in dose of GDC-0199 during the GDC-0199 dose ramp-up period.
- If the patient's ALC remains $\geq 25 \times 10^9$/L, they will remain in the high-risk category and continue to follow management guidelines for high-risk patients for subsequent dose increases of GDC-0199 during the GDC-0199 dose ramp-up period. Reassessment of the patient's risk category can occur prior to each subsequent dose increase.

Any patient who develops laboratory or clinical TLS meeting Cairo – Bishop criteria must have their GDC-0199 dose held until the electrolyte abnormalities resolve. The patient may resume dosing based on a risk assessment (including tumor burden status), as determined by the investigator.

First Rituximab Dose

For patients determined to be of low or medium risk for TLS:

- The first dose of rituximab may be given as an outpatient.
- TLS laboratory results must be reviewed prior to each dose and at 8 and 24 hours after initiating the rituximab infusion.
- If there is no evidence of TLS 24 hours after rituximab, patients can continue GDC-0199 dosing daily. The 24-hour chemistry values must be reviewed prior to the patient receiving the next day dose of GDC-0199.
- If any laboratory abnormalities consistent with TLS are observed, patients should undergo further management and monitoring as per the electrolyte management guideline in Appendix 12.

For patients who are at high risk of TLS:

- Patients will be hospitalized for rituximab infusion and for a minimum of 24 hours after initiation of rituximab.
- Hospitalized patients should receive TLS prophylaxis as for initial GDC-0199 dosing, including a uric acid reducer initiated 72 hours prior to infusion and IV hydration.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- Chemistries will be obtained prior to GDC-0199 and rituximab dose, and 4, 8 and 24 hours after initiation of rituximab infusion. Discharge of patient is dependent upon review of the 24-hour laboratory values by the investigator or designee.
- Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring as per Appendix 12, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome.

At the discretion of the investigator, patients categorized as high risk at baseline may undergo reimaging prior to initiation of rituximab. If all nodes are documented to be <10 cm, rituximab may be given as an outpatient. For patients who are deemed to be high risk due to LN ≥ 5 cm and ALC $\geq 25 \times 10^9$/L, if ALC is documented to be $<25 \times 10^9$/L at the time of rituximab infusion, rituximab may be given as an outpatient.

Statistical Methods

Primary Analysis

Efficacy

The primary efficacy endpoint is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard iwCLL guidelines [Hallek et al. 2008]), or death from any cause, whichever comes first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of the last disease assessment. If no disease assessments were performed after the baseline visit, PFS will be censored at the time of randomization.

Treatment comparison will be made using a two-sided stratified log-rank test (0.05 significance level, appropriately adjusted for an interim analysis) stratified by 17p deletion status (yes/no), early or late relapse or progression after prior chemotherapy-containing therapy (within 12 months after monotherapy or within 24 months after chemoimmunotherapy versus more than 12 months or 24 months after either), and geographic region (U.S./Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America). If the null hypothesis is rejected and the observed hazard ratio is favorable for the GDC-0199+R combination, then it is shown that GDC-0199+R has significantly longer PFS than BR.

If the study meets its primary endpoint of prolonging PFS assessed by the investigator in the overall study population, then a formal statistical test of PFS as assessed by the IRC between

the two arms will be performed at the 0.05 level for the population of patients determined to have 17p deletion. If the study does not meet its primary endpoint, then this test will not be performed. This fixed-sequence testing of the endpoint of PFS in 17p-deleted patients maintains the type I error level at 0.05.

Other analyses of secondary endpoints will not be tested formally, and there is no type I error control for these endpoints.

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients who were not reported as having died at the time of the analysis will be censored at the date when they were last known to be alive as documented by the investigator.

Duration of response is defined for patients with a CR or PR as the time from the date of the initial response (CR or PR) to the date of progression/relapse or death from any cause. For patients achieving a response who have not progressed, relapsed, or died at the time of analysis, DOR will be censored on the date of last disease assessment.

Time to next anti-CLL treatment is defined as the time from the date of randomization to the start date of the next anti-CLL treatment or death from any cause. For patients who have not received the next anti-lymphoma treatment or died at the time of analysis, TTNT will be censored at the date when the patient was last known to be alive without having received additional anti-lymphoma treatment.

Time-to-event endpoints such as OS, DOR, and TTNT will be analyzed using the same statistical methods described for the primary analysis of PFS.

Response rates in the treatment groups will be compared using stratified Cochran – Mantel – Haenszel (CMH) tests. Stratification factors are identical to those used for the primary endpoint. Rates and 95% confidence intervals will be reported for each treatment group.

Safety

The safety analyses will include all randomized patients who received at least one dose of study treatment (GDC-0199, rituximab, or bendamustine), with patients grouped according to the treatment actually received.

Treatment exposure will be summarized, including the number of cycles received by each patient, and the cumulative dose will be summarized by treatment arm.

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. All AEs occurring during or after the first treatment will be summarized by treatment arm and NCI CTCAE grade. In addition, all SAEs will be summarized.

Deaths reported during the study treatment period and those reported after treatment completion/discontinuation will be summarized by treatment arm.

Adverse events leading to early treatment discontinuation and early study withdrawal will be summarized by arm and reason.

Laboratory data with values outside of the normal ranges will be identified. Additionally, select laboratory data will be summarized by treatment arm and grade using the NCI CTCAE. Of note, abnormal laboratory data that are clinically significant will be reported as AEs and summarized in the AE tables.

Vital signs and other physical findings will be summarized by treatment arm.

Pharmacodynamics

The exploratory pharmacodynamic biomarker analyses will include patients with at least one pre-dose and/or one post-dose biomarker assessment, with patients grouped according to the treatment actually received.

Blood samples for biomarker assessments will be assayed using analytically qualified methods (eg, immunohistochemistry, ELISA, quantitative real-time polymerase chain reaction, and fluorescence-activated cell sorting).

Pharmacokinetics

Population PK methods will be used to characterize the PK of GDC-0199 in this study in conjunction with appropriate historical data. Potential correlations of exposure with dose, demographics, pharmacodynamic variables, safety, and efficacy outcomes may be explored as warranted by the data.

Patient-Reported Outcomes

Scoring for the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 questionnaires will be based on their corresponding user manuals (Fayers et al. 1999, Cleeland 2010). For the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales with more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

Summary statistics of the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales and their changes from baseline will be calculated at each assessment time point for both study arms.

Disease-related symptom progression will be measured by EORTC QLQ-C30 and EORTC QLQ-CLL questionnaires. Time-to-event Kaplan – Meier analysis on CLL symptoms will be used to demonstrate the time from first treatment to worsening in disease-related symptoms. An event is a change in symptom score by 10 points or more as defined as being clinically important.

Health Economics

Health economic data, as assessed by the EQ-5D, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D assessment that generate a score. Scores at baseline and change from baseline scores for each time point will be quantified using descriptive statistics.

Determination of Sample Size

The primary endpoint of PFS was used to determine the sample size for the study. Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- two-sided log-rank test at the 0.05 level of significance
- 80% power to detect a hazard ratio (HR) for GDC-0199+R versus BR of 0.66, corresponding to an approximate median improvement of 12.3 months to 23 months (34% reduction in risk of a PFS event)
- exponential distribution of PFS
- an annual dropout rate of 5%
- one interim analysis for efficacy, 12 months after the last patient enrolled

With these assumptions, 186 PFS events are required to achieve 80% power for the primary analysis of PFS in all patients. Assuming an enrollment of 20 months, it is planned to enroll 370 patients across two arms, randomized 1:1.

Interim Analyses

One interim analysis for efficacy of the primary endpoint of investigator-assessed PFS is planned. The interim analysis will be conducted 12 months after the last patient has been enrolled. Testing for efficacy at the interim analysis will occur at two-sided p value of 0.001. If the p value of the two-sided log-rank test is less than 0.001, the trial will have met its primary efficacy endpoint (corresponding to an observed hazard ratio of approximately 0.60 or better). Note that the interim analysis for efficacy is not based on fixed information fraction. If the total number of investigator-assessed PFS events across both arms exceeds 160 (approximately 86% information) or more at the time of the planned interim analysis, then the interim analysis will not be performed, and only the final analysis will be conducted.

The boundary for efficacy will be p value of 0.001. The final analysis will be performed after 186 events have occurred. The level will be adjusted to incorporate the alpha spent at the interim analysis, so that the overall two-sided type I error rate will be maintained at the 0.05 level.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
ASCT	allogeneic stem cell transplantation
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
AST	aspartate aminotransferase
AUC	area under the concentration – time curve
AUC_{0-24}	area under the concentration – time curve from time 0 to 24 hours post dose
AUC_{inf}	area under the concentration – time curve from time 0 to infinity
BM	bone marrow
BR	bendamustine and rituximab
BSA	body surface area
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
ESMO	European Society for Medical Oncology
FCR	fludarabine, cyclophosphamide, rituximab
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FR	fludarabine, rituximab
G-CSF	granulocyte colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVcAB	hepatitis C virus core antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HRQoL	health-related quality of life
IBM	ideal body mass
ICH	International Conference on Harmonisation
IDCC	Independent Data Coordinating Center
IDMC	Independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous
iwCLL	international workshop on Chronic Lymphocytic Leukemia
LDH	lactate dehydrogenase
MDASI	M. D. Anderson Symptom Inventory
MDS	myelodysplastic syndrome
miRNA	microRNA
MRD	minimal residual disease
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-WG	National Cancer Institute Working Group
NHL	non-Hodgkin's lymphoma
OS	overall survival
PD	progressive disease
PE	polyethylene
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PUR	polyurethane
PVC	polyvinyl chloride
QD	once daily
RCR	Roche Clinical Repository
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
STD	severely toxic dose
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
TTNT	time to next anti-CLL treatment
ULN	upper limit of normal
USPI	United States Product Insert

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most common of the chronic leukemias, comprising 30% of all adult leukemias, with a median age at diagnosis of 72 years. CLL is a clonal disease of unknown etiology, characterized by the accumulation of mature B cells in blood, lymph nodes, spleen, liver, and bone marrow (BM).

Morphologically, CLL cells are relatively mature appearing but immunologically incompetent. About 95% of CLL is of B-cell origin (B-CLL) with a characteristic phenotype (CD5+, CD23+; weak surface expression of CD19, CD20, and CD79b; and IgM- or IgD-restricted). Chromosomal abnormalities of the leukemia cells are found in >80% of cases, with the most common being deletion 13q14 (incidence 55%), deletion 11q- (18%), trisomy 12 (16%), and deletion 17p (7%) (Döhner et al. 2000).

More than 50% of CLL patients are asymptomatic at diagnosis and require no treatment. Symptoms appear as the disease progresses. Treatment is initiated when a patient's disease becomes symptomatic or progressive as defined by the international workshop on Chronic Lymphocytic Leukemia (iwCLL)'s updated guidelines for diagnosis and treatment of CLL (Hallek et al. 2008).

Response rates to initial treatment are high, but relapsed or refractory disease is often characterized by resistance to chemotherapy (ie, fludarabine or alkylating agents). Relapsed disease is associated with a median survival between 15 and 44 months and is dependent on CLL risk status, time to relapse, and choice of regimen (Lamanna et al. 2006; Wierda et al. 2010; Badoux et al. 2011; Fischer et al. 2011). Rituximab is approved for the treatment of both previously treated and previously untreated CLL in combination with chemotherapy in Europe and with fludarabine and cyclophosphamide (FC) in the U.S. Besides the regimen of FC and rituximab (FCR), the combination regimen approved in the U.S., one of the more commonly used and active regimens in relapsed CLL is the combination of bendamustine and rituximab (BR). The BR regimen was demonstrated to have meaningful clinical activity in relapsed/refractory CLL patients with an observed overall response (OR) rate of 59% and a median progression-free survival (PFS) of 15.2 months (Fischer et al. 2011).

Despite recent progress, CLL remains incurable; therefore, there is a need for the development of new treatments, which could improve both response rate and the survival of these patients.

1.2 BACKGROUND ON GDC-0199

1.2.1 Bcl-2 Protein Family

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma (FL), where the t(14;18) chromosomal translocation results in significant overexpression of Bcl-2 protein in

B-cells. The Bcl-2 family of genes encodes a group of closely related proteins that exhibit pro- or anti-apoptotic activity and share up to four Bcl-2 homology domains (Korsmeyer 1999; Cory and Adams 2002; Borner 2003; Cory et al. 2003). Bcl-2 overexpression is a major contributor to the pathogenesis of several lymphoid malignancies and is overexpressed in acute and chronic leukemias.

In CLL cells, the microRNAs (miRNAs) miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2 (Calin et al. 2008). Although Bcl-2 expression levels are variable across patients, high expression of Bcl-2 (compared to normal white blood cells) is observed in CLL cells in ≥95% of CLL patients (unpublished data from phase II study of ABT4710n [navitoclax]).

Bcl-2 overexpression represents one common mechanism for evading apoptosis. However, CLL cells may concurrently express high levels of Bcl-2 prebound to pro-death proteins such as Bim, thus priming these cells for death such that treatment with a BH3 mimetic like GDC-0199 will rapidly drive them into apoptosis (Del Gaizo Moore et al. 2007, Del Gaizo Moore and Letai 2008). Nonclinical data in non-Hodgkin's lymphoma (NHL) cell lines support a model analogous to CLL, where higher levels of Bcl-2 expression correlate strongly with greater sensitivity to GDC-0199 (unpublished data, [redacted] CLL and many NHL cells are therefore dependent on high levels of Bcl-2 for survival, making them potentially attractive targets for GDC-0199. Furthermore, this sensitivity to Bcl-2 inhibition may provide the possibility for a chemotherapy-sparing option for CLL patients.

1.2.2 GDC-0199

1.2.2.1 GDC-0199 Nonclinical Activity and Pharmacokinetic Profile

GDC-0199 (synonymous with ABT-199 and referred to as GDC-0199 throughout the protocol) is a highly selective, orally available small-molecule Bcl-2 family protein inhibitor that binds with high affinity (dissociation constant [Ki]<0.10 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-X_L and Bcl-w (>480-fold and >2000-fold lower affinity than to Bcl-2, respectively). Overexpression of anti-apoptotic Bcl-2 family proteins is associated with resistance to chemotherapy, and antagonism of the action of these proteins might overcome resistance and enhance response to therapy. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

In vitro, GDC-0199 demonstrated broad cell-killing activity against a panel of lymphoma and leukemia cells including B-cell FLs, mantle cell lymphomas, diffuse large B-cell lymphomas (DLBCLs), and acute myeloid leukemias (AMLs). GDC-0199 was especially potent against cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to GDC-0199 than were wild-type cell lines.

GDC-0199 inhibited subcutaneous murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL) and NHL.

The pharmacokinetic (PK) profile of GDC-0199 was evaluated in multiple animal species. In mice, rats, monkeys, and dogs, low plasma clearance and low volumes of distribution characterized the GDC-0199 PK profile. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs. Food had a marked effect on the oral bioavailability in dogs.

GDC-0199 demonstrated high protein binding to human, rat, dog, and monkey plasma proteins ($>$99.9%). In rats, GDC-0199 was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Liver metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. GDC-0199 showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

In vitro, GDC-0199 is metabolized by CYP3A4 and is a moderate inhibitor of CYP2C8 and a potent inhibitor of CYP2C9. It is not a potent inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C19, or CYP2D6 (IC50$>$30 μM) and does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM.

See the ABT-199/GDC-0199 Investigator's Brochure for a detailed discussion of the nonclinical activity of GDC-0199.

1.2.2.2 GDC-0199 Nonclinical Toxicology

The nonclinical toxicology of GDC-0199 has been evaluated in repeat-dose studies of up to 4 weeks duration with once daily (QD) oral dosing and with up to 4- and 26-week recovery periods and 26-week recovery periods in mice and dogs, respectively. In addition, GDC-0199 has been tested in safety pharmacology studies (cardiovascular [CV], respiratory, and neurofunctional), and in genetic toxicity tests (Ames and in vitro chromosome aberrations assays). A severely toxic dose to 10% of rodents (STD_{10}) was not identified in mice up to and including the highest dose of 600 mg/kg/day (overall mean $AUC_{0\text{-}24}=91.5$ μg•h/mL and $C_{max}=7.2$ μg/mL). In dogs, the highest non-severely toxic dose (HNSTD) was 150 mg/kg/day but due to overlapping exposures between the mid- and high doses, the HNSTD was defined as the mid-dose of 50 mg/kg/day (overall mean $AUC_{0\text{-}24}=472$ μg•h/mL and $C_{max}=27.4$ μg/mL).

Consistent with expected pharmacological activity, GDC-0199 caused moderate-to-marked decreases in lymphocytes, including both T- and B-cell subsets, and corresponding lymphoid depletion was observed in the spleen, lymph nodes, gut-associated lymphoid tissue (mice), and Peyer's patches (dogs). In dogs, after 4$-$6 months of recovery, B-cell counts reversed non-dose-dependently to 25$-$111% of individual baseline (mean reversal to 54% of baseline average). T-cell subsets reversed more readily and showed more dose-dependence in recovery time and extent.

Additional hematological effects included reductions in red cell mass (hemoglobin, hematocrit) that were adverse at 600 mg/kg/day in mice and at 150 mg/kg in dogs.

In dogs, GDC-0199 produced severe decreases in the numbers of spermatogonia after 4 weeks of dosing, with progression to severe decreases in all germ cells in testes during the 4-week recovery period. The translatability of the findings to humans is unknown, but this change may be related to GDC-0199 pharmacology as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis (Olderied et al. 2001; Sugiyama et al. 2001; Yan et al. 2003).

In an anesthetized dog cardiovascular model given intravenous doses of GDC-0199, mild reductions in cardiac output (-11% to -19%) and myocardial contractility (dP/dt_{max}; -6% to -13%) were observed at plasma concentrations of ≥ 16 μg/mL and ≥ 32 μg/mL, respectively; however, no effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed in either the anesthetized dog study or conscious dog CV studies using telemeterized animals.

In an ongoing 9-month chronic toxicity study in dogs, change in the hair coat from normal to increased amounts of white hair was observed after 3 months of dosing at 6 or 20 mg/kg/day (mid- and high doses, respectively). Based on a similar finding of gray hair coat in Bcl-2 -/- null mice, the change in dog hair coat is likely to be an effect of Bcl-2 inhibition on melanocyte stem cells but potential effects on patients are unknown.

Other nonclinical findings in dogs included non-severe, cutaneous swelling at high dose, post-dose emesis, salivation, and fecal alterations during the dosing period. Microscopic findings of single-cell necrosis in the gall bladder epithelium, stomach, exocrine pancreas, and epididymides were considered to be an effect of Bcl-2 inhibition but were of minimal magnitude and associated with no loss of mucosal integrity.

There were no consistent effects on respiratory or neurological function, and both in vitro genetic toxicity tests were negative.

See the ABT-199/GDC-0199 Investigator's Brochure for details on the nonclinical studies.

1.2.2.3 GDC-0199 Clinical Experience

The first-in-human GDC-0199 monotherapy dose-escalation study (Study M12-175) is ongoing in patients with relapsed or refractory CLL/small lymphocytic lymphoma (SLL) and NHL. Study M13-365 (GDC-0199 in combination with rituximab in relapsed/ refractory CLL) and Study GP28331 (GDC-0199 in combination with obinutuzumab) are also ongoing. As of January 11, 2013, 77 patients with relapsed/refractory CLL have been treated with GDC-0199 across three studies (56 patients in M12-175, 17 patients in M13-365, and 4 patients in GP28331 [redacted]). Preliminary safety, PK, and efficacy data are summarized below based on data cut-off dates of

January 11, 2013 for safety listings (see the ABT-199/GDC-0199 Investigator's Brochure for details on clinical studies). Dose-limiting toxicity (DLT) assessments are available for patients enrolled in Study M12-175 (through Cohort 8 with a target GDC-0199 dose of 1200 mg) and in Study M13-365 (through Cohort 3 with a target GDC-0199 dose of 400 mg).

Study M12-175 includes relapsed/refractory CLL/SLL and NHL patients with measurable disease, ECOG performance status ≤ 1, and adequate marrow function, who are enrolled to Arm A (CLL/SLL) or Arm B (NHL). Patients receive a single dose of GDC-0199 on Day -7 followed by continuous QD dosing from Day 1 until progressive disease or unacceptable toxicity.

Study M13-365 includes relapsed/refractory CLL patients with measurable disease, ECOG performance status ≤ 1, and adequate bone marrow function. Patients received GDC-0199 starting at 50 mg/day and were dose-escalated to the target cohort dose of GDC-0199 over three weeks followed by continuous daily dosing of GDC-0199 at the target cohort dose until disease progression. Rituximab was administered starting on Week 4, Day 1 at 375 mg/m^2 (the dose could be split over Cycle 1, Days 1 and 2 at the discretion of the investigator) followed by subsequent administrations of rituximab at 500 mg/m^2 on Day 1 of Weeks 5, 6, 10, 14, 18, 22, and 26.

Study GP28331 includes patients with relapsed/refractory CLL and measurable disease and adequate bone marrow function. Patients received either GDC-0199 starting at 50 mg/day and escalating to target dose over 3 weeks before initiating obinutuzumab, or obinutuzumab weekly for 3 doses with GDC-0199 starting on Day 9. Obinutuzumab was administered at a dose of 1000 mg, with the first dose split over 2 days.

1.2.2.3.1 Preliminary Safety Data Summary

This section summarizes safety events observed in patients with relapsed/refractory CLL enrolled in Studies M12-175, M13-365 and GP28331. See the ABT-199/GDC-0199 Investigator's Brochure for details. A detailed description of laboratory and clinical tumor lysis syndrome (TLS) events is presented in Section 1.2.2.3.2.

Data on GDC-0199 and human pregnancy or GDC-0199 and drug abuse/drug dependency are not available.

Study M12-175

Preliminary safety data as of January 11, 2013 for 56 patients with CLL/SLL enrolled in Study M12-175 with a median follow-up time of 190 days on study are summarized below. The data include patients treated at dose-escalation cohorts with target doses from 50 to 1200 mg of GDC-0199.

The most common adverse events (AEs), occurring in $>15\%$ of patients, were neutropenia (39%), nausea (36%), diarrhea (30%), fatigue (25%), upper respiratory tract

infection (23%), and cough (16%). Grade 3/4 AEs occurring in more than five patients were neutropenia (21 patients, 38%) and TLS (6 patients, 11%). The most frequently reported (>10%) AEs considered possibly or probably related to GDC-0199 include neutropenia (21 patients, 37%), nausea (13 patients, 23%), diarrhea (11 patients, 20%), fatigue (8 patients, 14%), thrombocytopenia (7 patients, 12%), and TLS (6 patients, 11%).

Serious adverse events (SAEs) were reported in 22 patients (39%). Those reported in more than one patient were TLS (4 patients, 7%), febrile neutropenia (3 patients, 5%), and autoimmune thrombocytopenia (2 patients, 4%). One serious adverse event resulted in death: a patient with an ongoing event of TLS at the time experienced sudden death (see Section 1.2.2.3.2 for details).

A total of three patients (5%) experienced adverse events that led to death: multi-organ failure, sudden death, and mental status changes, in one patient each.

A total of six patients (11%) experienced adverse events that led to study discontinuation: thrombocytopenia, general physical health deterioration, sudden death, TLS, and esophageal adenocarcinoma in one patient each, and diarrhea and vomiting in one additional patient.

In addition, Richter's transformation had been noted at the time of disease progression for six CLL patients. See the ABT-199/GDC-0199 Investigator's Brochure for more details on these patients.

Study M13-365

As of January 11, 2013, preliminary safety results are available for all 17 patients enrolled in Study M13-365. Six patients were enrolled in Cohort 1 (designated GDC-0199 cohort dose of 200 mg), ten patients were enrolled in Cohort 2 (designated GDC-0199 cohort dose of 300 mg), and one patient was enrolled in Cohort 3 (designated GDC-0199 cohort dose of 400 mg). Most patients (16 of 17, 94%) reported at least one treatment-emergent adverse event. The most common AEs were neutropenia (9 patients, 53%), nausea (7 patients, 41%), and thrombocytopenia, diarrhea, and pyrexia (4 patients each, 23%).

Eleven patients (65%) reported Grade≥3 adverse events. The most commonly reported Grade≥3 AEs occurring in more than one patient were neutropenia (8 patients, 47%), and thrombocytopenia, hyperkalemia, and TLS (2 patients each, 12%). Serious adverse events were reported in five patients (29%): TLS was reported in two patients (12%), and pyrexia, rotavirus infection, infusion-related reaction, hyperkalemia, histiocytosis hematophagic, and lymphoma transformation were reported in one patient each (6%). Both events of TLS as well as the individual events of rotavirus infection and hyperkalemia were considered by the investigator to be possibly or probably related to GDC-0199.

As described above, one patient experienced a serious adverse event of hyperkalemia in a setting of TLS that resulted in study discontinuation and death (see Section 1.2.2.3.2). Two additional patients experienced adverse events that resulted in discontinuation of GDC-0199 (thrombocytopenia and lymphoma transformation, respectively). The event of lymphoma transformation (Richter's transformation) was biopsy-confirmed DLBCL and was reported 13 days after the last dose of GDC-0199 and rituximab.

Study GP28331

In Study GP28331, four patients received study treatment; three received GDC-0199 for between 3 and 15 days, and one patient received obinutuzumab and a single dose of GDC-0199. All patients discontinued therapy after the TLS-related deaths in the other clinical studies. In this study, the only reported adverse event related to GDC-0199 was a serious event of hyperphosphatemia in the setting of laboratory TLS that occurred after the third dose of GDC-0199 in a patient who had not received obinutuzumab. The event resolved with intravenous hydration and discontinuation of study therapy.

1.2.2.3.2 Summary of TLS Events in CLL Patients with GDC-0199

In Study M12-175, substantial antitumor activity was observed in the first three patients with CLL following a single dose of GDC-0199 of 100 to 200 mg. Within 24 hours, dramatic reductions in lymphocyte count (>95%) were observed in the two patients with pretreatment lymphocytosis, and laboratory TLS developed in all three patients (per Cairo–Bishop Criteria [Appendix 10]; please see the ABT-199/GDC-0199 Investigator's Brochure for details regarding these patients). The TLS resolved without clinical complications in all three patients, and the patients were able to commence daily dosing of GDC-0199 at reduced doses (50 to 100 mg) within 7 days and later escalated to the target cohort dose of 200 mg.

Subsequently, changes to the GDC-0199 dose and schedule were implemented to obtain a more gradual tumor response and reduce the risk of TLS. The initial GDC-0199 dose was reduced to 50 mg (with the option of administering doses less than 50 mg in subjects with bulky disease and lymphocytosis) and 2 to 3 weekly escalation steps were introduced to reach the final cohort dose. Intensified monitoring and standard TLS prophylaxis measures including hydration and treatment to prevent hyperuricemia have been mandated in all patients. In the subsequent seven cohorts, 53 patients with CLL/SLL were enrolled. In Cohort 2, one of six patients showed only laboratory (chemical) changes in potassium and phosphate. The electrolyte changes were not considered clinically significant, and the patient received GDC-0199 without delay or dose reduction and without clinical sequelae. In Cohort 4, a serious adverse event of clinical TLS (considered related to GDC-0199) was reported after the initial dose of 50 mg GDC-0199. [redacted]

In , two fatal adverse events in the setting of TLS were reported. The first death occurred in Study M13-365 within 24 hours of the patient receiving a first dose of 50 mg GDC-0199. This patient had not yet received a dose of rituximab. The second death occurred in a patient in Study M12-175 after escalation to the 1200 mg GDC-0199 dose.

Following the two fatal events in , the dose of GDC-0199 was reduced in all active patients to 600 mg or less. Overall, six DLTs of TLS and two DLTs of fatalities in the setting of TLS were reported in the GDC-0199 clinical program (Arm A of Study M12-175, and Study M13-365). Details of these events are provided in the ABT-199/GDC-0199 Investigator's Brochure. Additional measures to minimize the risk of TLS have been implemented in the present protocol, including gradual step-up dosing, intensive monitoring, detailed management guidelines, and rigorous TLS prophylaxis (see Section 4.4.1.2).

Details of TLS events associated with GDC-0199 are provided in the ABT-199/ GDC-0199 Investigator's Brochure.

1.2.2.3.3 Preliminary Activity in CLL/SLL Patients

Study M12-175

As of January 11, 2013, preliminary activity data are available for 54 of 56 patients in Study M12-275 with relapsed or refractory CLL/SLL who have received GDC-0199. Patients remained on study for a median of 190 days (range 1 – 495 days). In particular, among 16 patients harboring 17p deletion enrolled in the study, the median time on study is 159 days (range 33 – 495 days). Forty-three patients remain on study, and 13 patients have discontinued: seven patients due to disease progression, and six patients for other reasons (2 patients with TLS, 2 patients with other illness, 1 patient required warfarin [prohibited because of potential drug – drug interaction] for a thromboembolic event, and 1 patient withdrew consent).

Response data are reported as best response documented while on study. An objective response was reported as best response in 46 of 54 evaluable patients in Arm A: five patients (8.9%) achieved complete response (CR), two patients (3.7%) achieved complete response with incomplete marrow recovery (CRi), and 39 patients (72.2%)

achieved partial response (PR). Among 16 patients harboring 17p deletion, objective response was reported in 14 patients (87.5%): one patient (6.3%) achieved CRi, and 13 patients (81.2%) achieved PR.

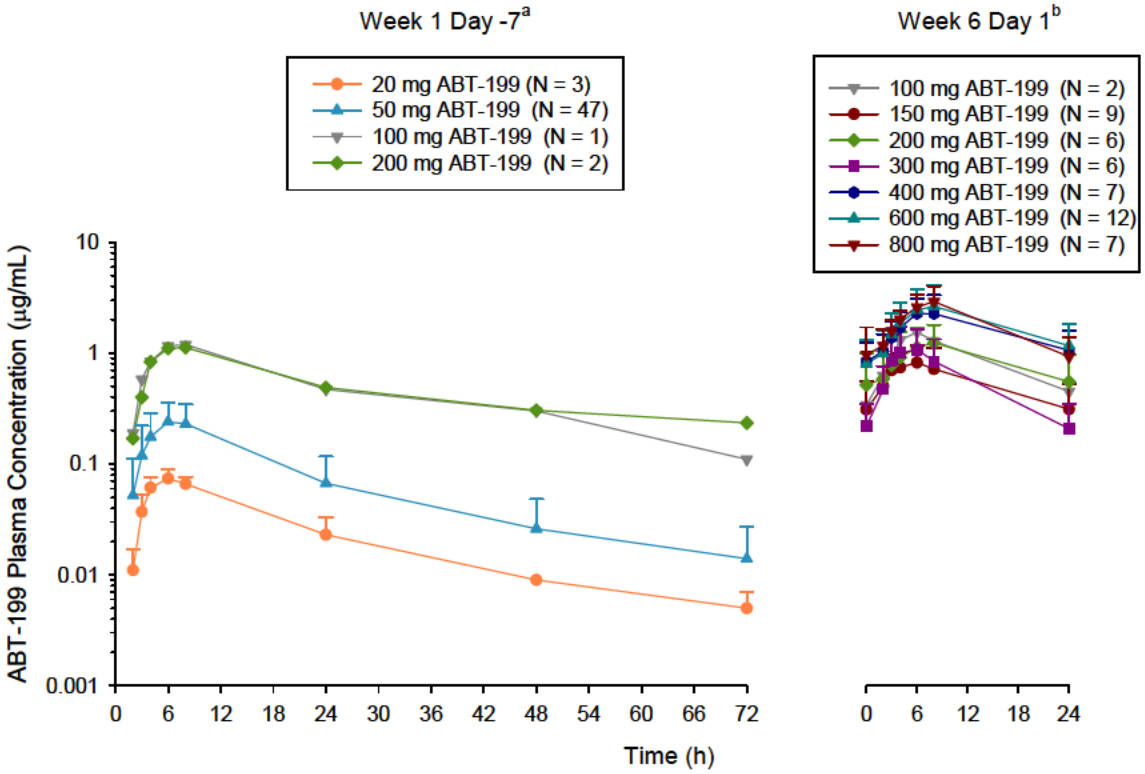
Study M13-365

Response data are not yet available for patients enrolled in Study M13-365.

1.2.2.4 Clinical Pharmacokinetics and Pharmacodynamics

Preliminary PK results are available from 53 patients with relapsed/refractory CLL/SLL from Study M12-175. The plasma concentration – time profiles of GDC-0199 in CLL/SLL patients are presented in Figure 1 following multiple doses of GDC-0199 at Day –7 (single dose) and Week 6 Day 1.

Figure 1 Study M12-175: Preliminary Mean (+SD) GDC-0199 Plasma Concentration–Time Profiles Following Oral Administration of GDC-0199 (ABT-199) in Patients with CLL/SLL (Log-Linear Scale)



All patients were dosed under low-fat conditions.

a Single dose. Combined data from Week 1 Day –3 (Cohort 1) and Week 1 Day –7 (subsequent cohorts).

b Steady state. Combined data from Week 3 Day 1 (Cohort 1) and Week 6 Day 1 (subsequent cohorts).

In CLL/SLL patients, all GDC-0199 doses were orally administered after a low-fat breakfast. The absorption of GDC-0199 was relatively slow. GDC-0199 plasma concentrations peaked at approximately 6 hours after dosing. The mean terminal phase

elimination half-life of GDC-0199 was approximately 17 h, and the mean oral clearance was approximately 13 L/h after a single dose.

The principal pharmacodynamic effect of GDC-0199 is lymphocyte depletion. All of the 11 CLL patients who had elevated lymphocyte counts pretreatment had >50% reduction in peripheral blood lymphocyte counts after treatment (median reduction 86% [range 59 – 99%]).

CLL cells collected 6 – 8 hours after initial dosing of GDC-0199 show increased Annexin-BB staining and caspase-3 activation (Roberts et al. 2012), consistent with a mechanism of action based on Bcl-2 inhibition.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Despite the progress made in the treatment of patients with CLL, a significant number of patients experience relapsed disease that is associated with progressively shorter durations of response to therapy. Patients with disease that is refractory to upfront treatment are at a similar disadvantage. The only potentially curative strategy for CLL is an allogeneic hematopoietic stem cell transplantation for which the majority of CLL patients are not eligible secondary to age or comorbid conditions. Improved treatment options are therefore critically important for this population.

Rituximab has been shown to be an effective treatment for low-grade, CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy. Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20, a hydrophobic, transmembrane protein that is present on the cell surface of pre-B-lymphocytes and mature B-lymphocytes but not on hematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissue. In particular, CD20 is present on malignant B-lymphocytes in the majority of patients with mature B-cell lymphomas and leukemias. The binding of rituximab to CD20 on B-lymphocytes eliminates these cells via a number of different possible mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis (Maloney et al. 2002).

Single-agent activity of rituximab with the use of a standard NHL dose has been marginal in CLL subjects (Nguyen et al. 1999). However, in the past decade, more intensive doses and schedules of rituximab have been explored and which demonstrated a good safety profile and significant activity in CLL (Byrd 2003; Hainsworth et al. 2003; Ferrajoli et al. 2011).

Studies in B-cell CLL patients treated with rituximab have shown a correlation with caspase activation and the depletion of B-lymphocytes, linking efficacy of this agent to activation of the intrinsic apoptotic pathway (Byrd et al. 2002). In vitro, rituximab-resistant lymphoma clones have recently been shown to up-regulate pro-survival Bcl-2 family members relative to wild-type cells and to exhibit a higher degree of resistance to

numerous chemotherapeutic agents. Cutaneous B-cell lymphoma samples obtained after clinical relapse from rituximab treatment also exhibited a strong up-regulation of Bcl-2 compared to those before therapy, potentially linking anti-apoptotic Bcl-2 proteins to therapy resistance (Wobser et al. 2007). These data suggest that by lowering the apoptotic threshold, a Bcl-2 antagonist may act synergistically with rituximab in a variety of settings.

GDC-0199 inhibits subcutaneous xenograft growth of human tumor cell lines derived from ALL and NHL and is highly efficacious using various doses and regimens. GDC-0199 enhanced the activity of a broad variety of chemotherapeutic agents (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; BR; and bortezomib) in other human hematological models (see the ABT-199/GDC-0199 Investigator's Brochure).

In a xenograft model of NHL (DoHH-2), GDC-0199 dosed as monotherapy caused significant tumor growth delay compared to the vehicle. Combining rituximab with GDC-0199 resulted in significantly ($p < 0.001$) improved tumor inhibition compared with GDC-0199 dosed as monotherapy (Genentech Report No. 10/974).

The unique mechanism of action of GDC-0199 suggests that it may represent a novel approach to targeting CLL. To date, the efficacy data from the single-agent phase I dose-escalation Study M12-175 suggest that the majority of patients respond to treatment with GDC-0199. Furthermore, combining GDC-0199 with rituximab in a chemotherapy-free regimen may be a more tolerable therapy for this generally older population.

As TLS is a special concern in patients treated with GDC-0199, intense monitoring requirements (including hospitalizations and frequent laboratory assessments) have been incorporated into this protocol; please see Section 4.4.1.2 (which includes a description of patients at low, medium, and high risk for developing TLS following treatment with GDC-0199), as well as Appendices 1 and 12 for monitoring guidelines.

Details regarding the safety monitoring plan for other potential risks associated with GDC-0199 are described in Section 5. Although the clinical experience with GDC-0199 in humans is limited, the safety data available to date suggest that toxicity with repeated dosing is acceptable.

Bendamustine and rituximab were selected as the comparator arm for this study as it is considered to be an efficacious regimen for relapsed CLL, as described in a phase II trial of relapsed/refractory patients; specifically, patients were treated with therapies as disparate as single-agent chemotherapy and multi-agent chemoimmunotherapy (Fischer et al. 2011). There is no uniform opinion on treatment of relapsed/refractory CLL; however, BR is considered a reasonable option per the National Comprehensive Cancer Network (NCCN) guidelines, the European Society for Medical Oncology (ESMO)

guidelines (Appendix 8), and a recent international consensus statement (Cheson et al. 2010). The limitations of BR include the toxicities of myelosuppression and infections (Fischer et al. 2011).

Since relapsed/refractory CLL represents an incurable disease for the majority of patients, there exists a need to introduce new agents that may improve clinical outcomes. The mechanism of action of GDC-0199 along with the available nonclinical and phase I data suggest that GDC-0199 may represent a more effective treatment option than current standard regimens. A treatment regimen that is demonstrated in a phase III setting to provide a clinically meaningful increase in PFS with similar or reduced toxicity compared with BR would be considered by investigators to provide a clinically beneficial option for patients. The precautionary safety measures including the enhanced TLS risk mitigation processes in place and regular monitoring of safety in the study by an Independent Data Monitoring Committee (IDMC) and by the Sponsor enables early identification of safety signals and minimizes the risk to patients enrolled. In conclusion, it is considered that the potential for benefit – risk ratio for this study is favorable.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of GDC-0199 and rituximab (GDC-0199+R) compared with bendamustine and rituximab (BR) in patients with relapsed or refractory CLL as measured by investigator-assessed PFS.

The secondary efficacy objectives for this study are as follows:

- To analyze Independent Review Committee (IRC)-assessed PFS in the subset of CLL patients with 17p deletion identified by fluorescence in situ hybridization (FISH) testing performed at a central laboratory.
- To evaluate PFS as assessed by an IRC.
- To analyze investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by fluorescence in situ hybridization (FISH) testing performed at a central laboratory.
- To evaluate rates of overall response (OR; defined as complete response [CR], complete response with incomplete marrow recovery [CRi], and partial response [PR]), PR, and CR and CRi at 12 weeks after Day 1 of the last cycle of multi-agent therapy, as assessed by the investigator.
- To evaluate OR, PR, CR, and CRi rates 12 weeks after Day 1 of the last cycle of multi-agent therapy, as determined by the IRC.
- To evaluate PFS as assessed by the investigator and by the IRC.
- To evaluate overall survival (OS).

- To evaluate duration of response (DOR) for patients with a best overall response of CR, CRi, or PR.
- To evaluate time to next anti-CLL treatment (TTNT).
- To evaluate the proportion of patients with minimal residual disease (MRD)-negativity at the disease response assessment time points.

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of GDC-0199 and rituximab compared with BR in patients with relapsed or refractory CLL, focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities.

2.3 PHARMACODYNAMIC OBJECTIVES

The pharmacodynamic objective for this study is to assess changes in lymphocyte subset counts during the study (eg, T and B cells).

2.4 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the pharmacokinetics of GDC-0199 in patients with relapsed or refractory CLL.

2.5 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- To compare treatment-related symptoms following treatment with GDC-0199 and rituximab compared with BR in patients with relapsed or refractory CLL, as measured by M. D. Anderson Symptom Inventory (MDASI) and European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and associated CLL module (QLQ-CLL16).
- To evaluate changes from baseline CLL symptoms scores using MDASI and EORTC QLQ-C30 and QLQ-CLL16 questionnaires.
- To evaluate time to disease-related symptom progression using EORTC QLQ-CLL16 health-related quality of life (HRQoL) using global health status/quality of life (QoL) and other functional subscales of QLQ-C30.
- To assess interference of treatment and disease-related symptoms on QoL using the MDASI questionnaire.

2.6 HEALTH ECONOMIC OBJECTIVES

The health economic objective for the study is to compare the health economic effects of GDC-0199 in combination with rituximab versus BR in patients with relapsed or refractory CLL as measured by the EuroQol 5 Dimension (EQ-5D) questionnaire (Rabin and deCharro 2001).

2.7 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the relationship between efficacy outcome and potential biomarkers, including Bcl-2 expression, for patients treated with GDC-0199 and rituximab compared with BR.
- To evaluate potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with GDC-0199 and rituximab or with BR.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is an open-label, international, multicenter, randomized, phase III study to investigate the efficacy and safety of GDC-0199 in combination with rituximab (GDC-0199+R) compared with bendamustine in combination with rituximab (BR) in patients with relapsed or refractory CLL.

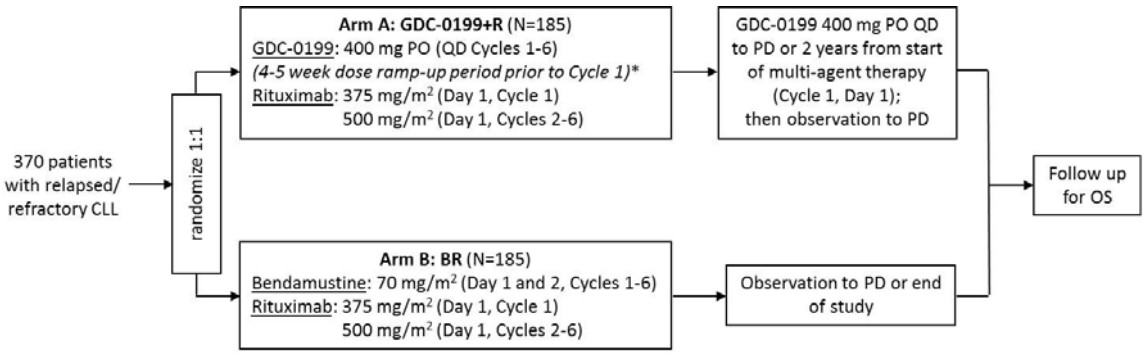
Approximately 370 patients will be recruited from approximately 150 centers in up to 29 countries and randomly assigned in 1:1 ratio to receive either GDC-0199+R (Arm A) or BR (Arm B). Randomization will be stratified according to the following factors:

- 17p deletion: yes or no
- risk status: high risk or low risk
  - high risk: defined as harboring 17p deletion or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy
  - low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemotherapy or chemoimmunotherapy.
- geographic region: U.S./Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America.

Patients randomized to Arm A (GDC-199+R) will have a 4 – 5 week GDC-0199 dose ramp-up period to reach the target dose of 400 mg daily. Following the GDC-0199 ramp-up period, patients will receive 6 cycles of rituximab consisting of a single infusion on the first day of each 28-day cycle. Patients will continue to take their daily dose of GDC-0199 during the rituximab cycles. Patients who have not progressed following the completion of the 6 cycles will continue to receive GDC-0199 until disease progression or for a maximum of 2 years from Cycle 1 Day 1.

Patients randomized to Arm B (BR) will receive 6 cycles of BR consisting of a single infusion of rituximab on Day 1 and bendamustine infusions on Days 1 and 2 of each 28-day cycle. After completion of the 6 cycles, patients will continue to be followed up until progression or study end.

Figure 2 Study Schema



Arm A: GDC-0199 and rituximab (GDC-0199+R); Arm B: bendamustine and rituximab (BR). 1 cycle = 28 days. CLL: chronic lymphocytic leukemia; OS: overall survival; PD: progressive disease; PO: per os; QD: once daily.

* Patients will receive GDC-0199 starting on Day 1 (GDC-0199 dose ramp-up period) as delineated in Section 4.3.2.1.1. There is a possibility that this dose ramp-up period may be one extra week longer to account for a possible continuation of the 20 mg test dose for 1 week prior to increasing the dose to 50 mg (see Section 4.3.2.1.1). In this case, the GDC-0199 ramp-up period would be 5 weeks (35 days). GDC-0199 will then be self-administered at 400 mg per day for a maximum of 2 years from Cycle 1, Day 1 or until disease progression (whichever is earlier). Multi-agent therapy consisting of 6 cycles of rituximab and daily GDC-0199 dosing will start after completion of the GDC-0199 ramp-up period.

All patients will be assessed for response to treatment by the investigator using standard clinical and laboratory examinations and CT scans according to iwCLL guidelines (Hallek et al. 2008) at screening and at the following time points (selected to mirror those used in current phase III CLL protocols [CLL10, CLL11]):

- interim assessment (within 14 days of Cycle 4, Day 1)
- at completion of multi-agent therapy (4 weeks ± 7 days after Day 1 of the last cycle of rituximab (Arm A) or BR (Arm B), clinical assessment only)
- 8 – 12 weeks after multi-agent therapy (defined as 8 – 12 weeks after Day 1 of Cycle 6 or 8 – 12 weeks after Day 1 of the last cycle for early termination).

Following 6 cycles of multi-agent therapy, patients in both arms who have not progressed will be followed clinically every 3 months through Year 3 from initiation of multi-agent therapy (Cycle 1, Day 1). Patients will then be followed every 6 months until disease progression, study withdrawal, or end of study, whichever comes first. At each follow-up visit, patients will be assessed for response/progression by physical examination and laboratory tests. In addition, at any time during follow-up when clinical or laboratory findings suggest that the response may have improved from stable disease (SD) to PR, or from PR to CR, imaging should be performed to confirm the response. Imaging is not routinely required to determine PD, as objective evidence of PD is most often documented by measurement of elevated peripheral CLL cells. However, when PD cannot be documented by increasing peripheral blood lymphocyte count, imaging is

required to document PD detected by physical examination or suspected based on symptoms.

After 5 years in the study or after disease progression (whichever comes first), patients will be followed annually for OS, PD, and new anti-CLL therapy until up to 3 years after the last patient is enrolled, withdrawal of consent, or the end of study, whichever comes first. Annual follow-up may be conducted by telephone contact.

Patients who discontinue all components of study therapy either prior to completion of planned therapy or prior to disease progression (eg, for toxicity) will continue to be followed for MRD levels, PD, and OS (regardless of whether they subsequently receive new anti-CLL therapy).

An independent review of the responses of all patients will also be conducted to confirm the primary PFS endpoint, including blinded review of clinical and laboratory findings as well as blinded radiology review of imaging assessments (see Section 3.1.2).

Safety will be evaluated by monitoring the nature/frequency/severity of SAEs and non-serious AEs, premature study withdrawals, deaths, effects on laboratory parameters, vital signs, physical examination, GDC-0199 dose delays, or effects on other safety biomarkers. Adverse events will be graded using NCI CTCAE, v4.0 (see Section 5.3.3). Laboratory safety assessments will include regular monitoring of hematology, blood chemistry, and tests of immunologic parameters.

Quality of Life will be assessed using the MDASI, EORTC QLQ-C30, and CLL-16 module scoring manuals (see Appendices 3, 4, and 5).

A schedule of assessments is provided in Appendix 1.

3.1.1 Independent Review Committee

An IRC composed of board-certified radiologists and board-certified oncologists with experience in CLL will assess in a blinded manner all patients for response and progression on the basis of imaging results, bone marrow biopsy results, and relevant clinical data, guided by a charter specific to the independent review.

3.1.2 Data Monitoring Committee

This trial includes an Independent Data Monitoring Committee (IDMC) for review of safety and efficacy data collected during the study. Reviews by the IDMC will be conducted according to a charter written and approved prior to study initiation. Members of the IDMC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities.

At the beginning of the study, intensive monitoring and analysis of all clinically significant safety events will be performed. The IDMC will assemble to review a safety analysis of

significant safety events approximately 1 month after the first patient is enrolled depending on the rate of initial patient enrollment, then approximately every 2 months until 40 patients have completed 2 cycles of treatment (with approximately 20 patients in each arm). Thereafter, the IDMC will meet approximately every 6 months and subsequently at a frequency determined by the IDMC and the Sponsor according to the emerging safety profile. In addition, either the Sponsor or the IDMC can request ad hoc IDMC meetings at any time that potential safety concerns arise. The IDMC will evaluate efficacy and safety at one formal interim analysis.

An Independent Data Coordinating Center (IDCC) that is independent of the Sponsor will prepare analyses for review.

3.2 END OF STUDY

The end of the study will be approximately 3 years after last patient is enrolled allowing for completion of the maximum duration of planned therapy (in the absence of disease progression) as well as at least one year of follow-up for all patients.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Combination Therapy (Experimental Group)

Rituximab has been shown to be an effective treatment for low-grade, CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy (Maloney et al. 2002; Cheson 2006).

Although the exact mechanism of action of rituximab remains unclear, it is known to induce cell death through several pathways including CDC, ADCC, and apoptosis (Maloney et al. 2002). In vitro, rituximab-resistant lymphoma clones have been shown to up-regulate pro-survival Bcl-2 family members relative to wild-type cells and to exhibit a higher degree of resistance to numerous chemotherapeutic agents. Cutaneous B-cell lymphoma samples obtained after clinical relapse from rituximab treatment also exhibited a strong up-regulation of Bcl-2 compared to those before therapy, potentially linking anti-apoptotic Bcl-2 proteins to therapy resistance (Wobser at al. 2007). These data suggest that by lowering the apoptotic threshold, a Bcl-2 antagonist may act synergistically with rituximab in a variety of settings.

In a xenograft model of NHL (DoHH-2), GDC-199 dosed as monotherapy caused significant tumor growth delay compared to the vehicle. Combining rituximab and bendamustine with GDC-0199 resulted in significantly improved tumor inhibition compared with rituximab and bendamustine alone (Souers et al. 2013). Therefore, this combination may hold promise in the treatment of CD20-positive lymphoid malignancies.

3.3.1.1 Rationale for GDC-0199 Dosage

GDC-0199 dosing for this study was based on the experience from the single-agent phase I dose-escalation Study M12-175 examining single-agent GDC-0199 in relapsed and refractory CLL patients. That study established a step-up schedule over several

weeks in order to safely administer GDC-0199, reducing the risk for TLS by more gradually reducing the leukemia cell burden prior to administration of the full target dose. The starting dose of GDC-0199 in the study is a 20 mg test dose followed (in the absence of laboratory evidence of TLS) by 50 mg GDC-0199 QD for the first week, followed by weekly increases in dose levels to a maximum dose of 600 mg. However, the dose to be used in combination with rituximab and other agents may be below the maximum dose established as a single agent. Preliminary data from Study M12-175 show that the 400 mg GDC-0199 dose as a single agent results in exposure that causes $>80\%$ reduction in lymphocyte counts, tumor size, and bone marrow infiltrates in most patients.

3.3.1.2 Rationale for Rituximab Dosage

The approved body surface area (BSA)-adjusted dosing regimen of rituximab in combination with chemotherapy for front-line or relapsed CLL will be used in this study: 375 mg/m^2 at Cycle 1 followed by 500 mg/m^2 at Cycles $2-6$ at intervals of 4 weeks. Evaluation of a potential PK interaction from the combination of GDC-0199 and rituximab is incorporated into the PK assessment plan in an ongoing study (M13-365).

3.3.1.3 Rationale for Duration of Therapy

The number of cycles of dosing (6×28-day cycles) is designed to provide a duration of treatment consistent with other therapies for CLL that have been shown to be sufficient to provide durable responses. Patients randomized to Arm A (GDC-0199+R) who have not had disease progression after 6 cycles of therapy will continue on daily GDC-0199 monotherapy until disease progression or for a maximum of 2 years from Cycle 1, Day 1. In the single-agent phase I dose-escalation Study M12-175, responses to single-agent GDC-0199 have been seen to improve over time as treatment continues without a fixed stopping point; thus, early termination of GDC-0199 treatment may prevent patients from reaching their maximal response. Treatment to progression is being evaluated in the phase I studies of GDC-0199; so far, no evidence of unexpected late toxicities has emerged from continued treatment with GDC-0199 beyond 6 months.

3.3.2 Rationale for Control Group

Bendamustine and rituximab (BR) is considered a relevant comparator arm, as other available recommended and/or approved therapies in this setting are either associated with high toxicity (eg, FCR, ASCT, high-dose steroid combinations, and alemtuzumab) or have limited effectiveness (eg, ofatumumab, rituximab monotherapy, or chlorambucil) (Eichhorst et al. 2011). Furthermore, BR is recommended as a second-line therapy for fit or elderly patients experiencing short durations of initial treatment response. In a phase II trial examining the efficacy of BR in relapsed/refractory CLL, median OS was 34 months and median PFS was 15 months (Fischer et al. 2011). Alemtuzumab is recommended for treatment of patients with 17p deletion per the NCCN Practice Guidelines in Oncology (v3.2012); however, it has been withdrawn from commercial availability in the US and the EU and will be available only under a compassionate use program for appropriate patients. Moreover, alemtuzumab is less effective for

eradication of bulky disease (Fiegl et al. 2006; Keating et al. 2002). While response rate to BR in relapsed CLL with 17p deletion is low, more effective alternatives are not universally available.

3.3.2.1 Rationale for BR Dosage

Two phase II single-arm studies have investigated BR in the previously untreated and in the relapsed/refractory CLL settings, respectively. In the previously untreated CLL study, bendamustine was dosed for 6 cycles at 90 mg/m^2 on Days 1 and 2 in combination with rituximab administered at 375 mg/m^2 for the first cycle and 500 mg/m^2 for Cycles 2 – 6 (Fischer et al. 2009). Preliminary results indicate an OR rate of 91%, with 33% CR rate.

In the relapsed/refractory CLL study, bendamustine was dosed for 6 cycles at 70 mg/m^2 on Days 1 and 2 when combined with rituximab administered at 375 mg/m^2 for the first cycle and 500 mg/m^2 for Cycles 2 – 6 (Fischer et al. 2011). In this study with 78 patients, the most common Grade 3/4 AEs observed included neutropenia (23%), thrombocytopenia (28%), and anemia (17%). Grade 3 infections occurred in 13% of patients; dose reductions were required in 37% of patients, and 23% and 44% of patients did not receive at least 3 or all 6 cycles of treatment, respectively, most often due to toxicity. Even with this safety profile, which is not unusual with chemoimmunotherapy regimens in this patient population, BR was demonstrated to have meaningful clinical activity with an OR rate of 59% and PFS of 15 months.

In the phase II study in relapsed/refractory CLL, rituximab was dosed at 375 mg/m^2 for the first cycle and at 500 mg/m^2 during Cycles 2 – 6 (Fischer et al. 2011). As this schedule resulted in meaningful clinical activity, the same schedule will be used in the BR arm for this study.

Bendamustine and rituximab chemoimmunotherapy has been shown to be associated with toxicity (eg, myelosuppression) that can necessitate dose delays, dose reductions, and early discontinuation in patients with NHL and CLL (Fischer et al. 2011). Consensus recommendations for bendamustine dose are 70 mg/m^2 in relapsed/refractory patients either as a single agent or in combination with rituximab (Cheson et al. 2010). Patients participating in this study will be treated according to this recommendation and will therefore receive 70 mg/m^2 bendamustine on Days 1 and 2 of the cycle for six cycles.

3.3.3 Rationale for Patient Population

Survival in CLL patients is highly variable, ranging from less than 2 years to 20 years or more (Binet et al. 1981). Intermediate-risk (Rai Stages I and II) patients, who account for 61% of all CLL patients, have a median survival of 7 – 9 years. High-risk (Rai Stages III and IV) patients, who account for 8% of all CLL patients, have a median survival of 5 years.

Treatment is usually initiated when the patient becomes symptomatic or progresses to late-stage CLL. First-line treatment of CLL has evolved from single-agent therapy to combination chemoimmunotherapy (Keating et al. 1993; Johnson et al. 1996; Rai et al. 2000; Leporrier et al. 2001; Eichhorst et al. 2006; Catovsky et al. 2007; Flinn et al. 2007; Hillmen et al. 2007; Hallek et al. 2010). The choice of front-line therapy is guided by patient age, comorbidity, and performance status. The lack of a standard regimen for front-line patients results in a heterogeneous population of second-line patients that has been documented in other studies in the relapsed/refractory setting (Fischer et al. 2011).

For relapsed patients, single- and multi-agent therapies are options but relapsed disease is associated with a median survival between 15 and 44 months and is highly dependent on CLL risk status and choice of regimen (Lamanna et al. 2006, Wierda et al. 2010; Fischer et al. 2011). Furthermore, the NCCN and ESMO guidelines list several options for treatment of relapsed patients (Appendix 8), which take into account the duration of initial response as response duration has been shown to be prognostic of long-term outcome (Tam et al. 2008). Allogeneic stem cell transplantation (ASCT) is the only potentially curative treatment option for CLL patients; however, transplantation is only appropriate for a small number of younger patients and is associated with high morbidity and mortality.

In this study, eligible patients must have been treated with at least one but no more than three previous lines of therapy (a line of therapy is defined as completing 2 cycles of treatment for a given line of therapy) including at least one prior standard chemotherapy-containing regimen according to current guidelines. Multiple standard and experimental treatments are available for CLL and vary by geographic region. Therefore, relapsed/refractory CLL patients represent a heterogeneous group especially as the number of prior therapies increases. In the present study, the number of previous therapies is limited to three in order to limit this heterogeneity.

Data from clinical trials of fit individuals treated with FCR chemotherapy in the front-line setting have demonstrated long-term durable responses (Tam et al. 2008; Hallek et al. 2010). As previously noted, similar responses for relapsed/refractory patients have not been observed. Therefore, novel approaches are needed to improve the outcome of this subset of CLL patients.

In almost all cases, CLL remains an incurable disease. Moreover, treatment options are limited in the largely elderly patient population. A chemotherapy-free regimen (eg, GDC-0199+R) may have fewer side effects and represent a novel strategy for improving response rates and the morbidity and mortality of patients with relapsed/refractory CLL.

3.3.4 Rationale for Including Patients with 17p Deletion

CLL patients with the 17p deletion (resulting in loss of the *p53* tumor suppressor allele) have a poor prognosis characterized by suboptimal responses to first-line and subsequent therapies. Defects in *p53* are found in approximately 10 – 15% of CLL patients requiring front-line therapy (Pettitt et al. 2012). Among patients with chemotherapy-refractory CLL, the frequency increases to almost 50% (Zenz et al. 2009).

There are currently no treatments approved specifically to meet the need of the 17p deletion population. For relapsed/refractory 17p deletion patients ineligible for allogeneic transplant or clinical trial, outcomes following standard therapy are significantly worse than for patients without abnormalities at 17p (Pettitt et al. 2012).

Among patients with relapsed CLL treated with FCR, those with the 17p deletion showed poorer outcomes than the overall study population. PFS and OS were 5 months and 10 months, respectively, in patients with 17p deletion, compared with 21 months and 47 months in the entire cohort. The corresponding response rates were also lower in patients with the 17p deletion (Badoux et al. 2011).

Pettitt et al. recently described the outcome of patients with the 17p deletion treated in the front-line setting or at relapse with alemtuzumab. Among the 22 relapsed patients, an OR rate of 77% was observed with a median PFS of 6.5 months (Pettitt et al. 2012). However, alemtuzumab and other approved therapies are associated with significant toxicity, limiting their use in older populations.

The mechanism of action of GDC-0199 is independent of the TP53 pathway. Early results from the ongoing single-agent phase I dose-escalation Study M12-175 have demonstrated activity in 14 of 16 relapsed/refractory CLL subjects with the 17p deletion. These encouraging preliminary data indicate that GDC-0199 may be beneficial in this unique high-risk patient population and may also represent a less toxic option as GDC-0199 is being used in combination with rituximab.

3.3.5 Rationale for Biomarker Assessments

GDC-0199 inhibits the ability of cancer cells to evade cell death, or apoptosis, by blocking the activity of the anti-apoptotic protein Bcl-2 (Korsmeyer 1999; Cory and Adams 2002; Borner 2003; Cory et al. 2003). Nonclinical studies have demonstrated a pattern of response to GDC-0199 based on the levels of Bcl-2 family proteins. High levels of Bcl-2 and low levels of Mcl-1 are generally predictive of response to this drug in vitro (unpublished data, Genentech, Inc.). In addition, high levels of at least one pro-apoptotic “sensor” such as Noxa or Bim is required. Furthermore, nonclinical studies have suggested that acquired rituximab resistance may occur as a result of the up-regulation of Bcl 2 (Byrd et al. 2002). Measurement of relevant RNAs, miRNAs, tumor-associated DNA alterations (such as p53 and Notch1 mutations) and proteins (including those in the Bcl-2 family) in CLL cells will be examined pre-treatment, on treatment, and at the time of progression for putative stratification markers and

correlation with efficacy. In addition, blood samples will be collected to determine in vitro sensitivity of CLL cells to GDC-0199 (EC50) to evaluate if response to GDC-0199 can be predicted in vitro. These studies will help to identify responsive patient populations and to develop better therapies for patients with CLL. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

3.3.6 Rationale for Patient-Reported Outcome Assessments

Patients with CLL experience a high symptom burden from the underlying disease process that is compounded by the side-effects of currently available therapies. These symptoms and treatment-related side-effects can impact function and, subsequently, health-related quality of life (HRQoL). If the expected clinical benefit of GDC-0199+R is observed in the trial, there is reason to believe that patients might observe an accompanying improvement in distinct key symptoms of the disease (ie, reduction in fatigue, reduction in nodular pain, and decrease in night sweats). Patient-reported outcomes (PROs) will be used to capture the patients' report of these symptom changes and detect change in disease symptoms. Specifically, with PFS being a primary clinical endpoint, understanding the time to disease progression through PROs and what patients gain from disease symptoms during this time can be used to support PFS.

To comprehensively characterize treatment-related side-effects between the two study arms, PROs will be used to evaluate common treatment-related side-effects. It is hoped that the novel treatment approach of GDC-0199+R will have a reduced side-effect profile and improved tolerability compared to traditional chemotherapy and result in an improvement in HRQoL and functioning for patients with CLL while undergoing treatment. The reduction in both disease symptoms and treatment-related side-effects combined with a subsequent improvement in HRQoL might serve to reduce health economic impact for these patients.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse, determined using standard iwCLL guidelines (Hallek et al. 2008), or death from any cause, whichever comes first.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- IRC-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory.
- IRC-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse, or death from any cause.

- Investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory.
- Overall response (OR; defined as complete response [CR], complete response with incomplete marrow recovery [CRi], and partial response [PR]), PR, and CR/CRi rates at 12 weeks after Day 1 of the last cycle of multi-agent therapy, as assessed by the investigator. Disease response will be assessed according to the iwCLL guidelines (Hallek et al. 2008).
- OR, PR, CR, and CRi rates 12 weeks after Day 1 of the last cycle of multi-agent therapy, as assessed by the IRC.
- Investigator-assessed PFS and IRC-assessed PFS.
- Overall survival (OS), defined as the time from randomization to death from any cause.
- Duration of response (DOR), defined for patients with a best OR of CR, CRi, or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse, as assessed by the investigator, or death from any cause.
- Time to next anti-CLL treatment (TTNT), defined as the time from randomization to start of new non-protocol anti-CLL therapy or death from any cause.
- Proportion of patients with minimal residual disease (MRD)-negativity at the disease response assessment time points as measured at a central laboratory on peripheral blood and/or BM samples.

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs).
- Changes in clinical laboratory results (including hematology and chemistry) during and following administration of study treatment.
- Incidence of AEs of special interest:
  - Grade ≥ 3 TLS and IRRs
- Measures of immune function, including serial immunoglobulin levels (IgG, IgM, IgA) following treatment with GDC-0199+R or BR.

3.4.3 Pharmacodynamic Outcome Measures

The pharmacodynamic outcome measure for this study is as follows:

- Serial assessment of B- and T-cell lymphocyte subsets by flow cytometry.

3.4.4 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Apparent clearance, apparent volume of distribution, and other appropriate PK parameters of GDC-0199 characterized using population PK techniques.

3.4.5 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- M. D. Anderson Symptom Inventory (MDASI).
- European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and associated CLL module (QLQ-CLL16).

3.4.6 Health Economic Outcome Measures

The health economic outcome measure for this study is as follows:

- The EuroQol 5-Dimension (EQ-5D) questionnaire.

3.4.7 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Evaluation of the relationship between response and PFS and various potential biomarkers, including Bcl-2 expression, for patients treated with GDC-0199+R or BR.
- Assessment of potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with GDC-0199+R or BR.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this study is adult patients with relapsed or refractory CLL requiring treatment.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent.
- Age $\geq$ 18 years.
- Diagnosis of CLL that meets published diagnostic criteria (Hallek et al. 2008). Patients must have peripheral blood B-lymphocyte counts which clonally express CD5, CD19/20, and CD23 and are either kappa or lambda light-chain-restricted. Pro-lymphocytes may comprise no more than 55% of total circulating lymphocytes. At initial diagnosis of CLL (ie, prior to front-line treatment), the peripheral lymphocyte count must have been $>5000/mm^3$. Patients must meet the following criteria for relapsed or refractory CLL (per the iwCLL guidelines [Hallek et al. 2008]):
  - Relapsed disease: a patient who previously achieved a CR or PR, but after a period of 6 months or more demonstrates evidence of progression;
  - Refractory disease: treatment failure or disease progression within 6 months of the last anti-leukemia therapy.
- Previously treated with at least one but not more than three lines of therapy (a line of therapy is defined as completing at least two cycles of treatment for a given line of therapy), including at least one prior standard chemotherapy-containing regimen according to current guidelines (Appendix 8).

- For patients with 17p deletion, previously treated with at least one but not more than three lines of therapy, including at least one prior standard chemotherapy-containing regimen according to current guidelines OR at least one prior alemtuzumab-containing therapy.
- Patients previously treated with bendamustine only if their duration of response was $\geq$24 months.
- Patient requires treatment in the opinion of the investigator.
- Eastern Cooperative Oncology Group (ECOG) performance score of $\leq$1 (see Appendix 7).
- Adequate BM function independent of growth factor or transfusion support, per local laboratory reference range at screening as follows:
  - platelet count $\geq$ 75 000/mm^3;
  - absolute neutrophil count (ANC) $\geq$1000/mm^3 unless cytopenia is clearly due to marrow involvement of CLL;
  - total hemoglobin $\geq$9 g/dL (without transfusion support within 2 weeks of screening);
  - if any of the above-mentioned cytopenias are present, there should be no evidence of myelodysplastic syndrome (MDS) or hypoplastic BM.
- Adequate renal and hepatic function, per laboratory reference range at screening as follows:
  - Calculated creatinine clearance $\geq$ 50 mL/min using 24-hour creatinine clearance or modified Cockcroft – Gault equation (using ideal body mass [IBM] instead of mass):

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

    Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/L})}$$

    IBM should be used:
    IBM (kg) = [(height in cm – 154) $\times$ 0.9] + (50 if male, 45.5 if female)
  - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 3.0 $\times$ the upper limit of normal (ULN) of the institution's normal range;
  - bilirubin $\leq$ 1.5 $\times$ ULN. Patients with Gilbert's syndrome may have a bilirubin level $>$ 1.5 $\times$ ULN, per discussion between the investigator and the Medical Monitor;
  - prothrombin time (or international normalized ratio) and partial thromboplastin time not to exceed 1.2 $\times$ the institution's normal range (patients with an elevated prothrombin time and known lupus anticoagulant may be eligible for participation after consulting the Medical Monitor).

- Female patients must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:
  - at screening, on a serum sample obtained within 14 days prior to initiation of study treatment, and
  - prior to dosing, on a urine sample obtained on Week 1 Day 1 if it has been >7 days since obtaining the serum pregnancy test result.
- Female patients who are not surgically sterile or postmenopausal (for at least 1 year) must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after completing therapy with rituximab:
  - total abstinence from sexual intercourse;
  - a vasectomized partner;
  - hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) that started at least 3 months prior to study drug administration;
  - double-barrier method (condom+diaphragm or cervical cup with spermicidal contraceptive sponge, jellies, or cream).
- Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after completing therapy with rituximab:
  - a partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration;
  - total abstinence from sexual intercourse;
  - double-barrier method (condom+diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream).

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Transformation of CLL to aggressive NHL (eg, Richter's transformation, prolymphocytic leukemia, or DLBCL) or CNS involvement by CLL.
- Undergone an allogeneic stem cell transplant.
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia.
- History of intolerance to prior bendamustine treatment (defined as toxicity requiring permanent discontinuation of bendamustine) or other contraindication to bendamustine treatment.
- History of severe (ie, requiring permanent discontinuation of prior rituximab therapy) prior allergic or anaphylactic reactions to rituximab.
- Known HIV-positivity.

- Positive hepatitis serology (serology testing required at screening), as follows:
  - Hepatitis B virus (HBV): Patients with positive serology for hepatitis B defined as positivity for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc).
  - Hepatitis C virus (HCV): Patients with positive hepatitis C serology unless HCV (RNA) is confirmed negative. Note that patients with HCV- or hepatitis C virus core antibody (HCVcAB)-positivity who have received recent IV IgG should be evaluated further for risk of viral reactivation and may be eligible for the study after discussion with the Medical Monitor.
- Requires the use of warfarin (due to potential drug – drug interactions that may potentially increase the exposure of warfarin). Patients may be eligible if able to be taken off warfarin and started on an alternative anticoagulant.
- Received an anti-CLL monoclonal antibody within 8 weeks prior to the first dose of study drug.
- Received any of the following agents within 14 days prior to the first dose of study drug, or has not recovered to less than Grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
  - any anti-cancer therapy including chemotherapy or radiotherapy and steroid therapy for anti-neoplastic intent;
  - investigational therapy, including targeted small-molecule agents.
- Received CYP3A4 inhibitors (such as fluconazole, ketoconazole, and clarithromycin) within 7 days prior to the first dose of GDC-0199 (see Appendix 9).
- Received potent CYP3A4 inducers (such as rifampin, carbamazepine, phenytoin, St. John's Wort) within 7 days prior to the first dose of GDC-0199 (see Appendix 9).
- History of prior GDC-0199 treatment.
- Consumed grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of GDC-0199.
- A cardiovascular disability status of New York Heart Association Class $\geq$3. Class 3 is defined as cardiac disease in which patients are comfortable at rest but marked limitation of physical activity due to fatigue, palpitations, dyspnea, or anginal pain.
- A significant history of renal, neurologic, psychiatric, endocrine, metabolic, immunologic, cardiovascular, or hepatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes.
- A female patient who is pregnant or breast-feeding.
- History of prior other malignancy that could affect compliance with the protocol or interpretation of results with the exception of the following:
  - curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study;

- other cancers not specified above which have been curatively treated by surgery and/or radiation therapy from which patient is disease-free for ≥5 years without further treatment.

- Malabsorption syndrome or other condition that precludes enteral route of administration.
- Known allergy to both xanthine oxidase inhibitors and rasburicase.
- Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal).
- Vaccination with a live vaccine within 28 days prior to randomization.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

Randomization will be performed by an interactive voice-/web-based system (IxRS). Patients will be assigned in 1:1 ratio to one of the two treatment arms through a block stratified randomization procedure. The randomization scheme will ensure approximately equal sample sizes in the two treatment groups in regard to the following stratification factors:

- 17p deletion by local testing (yes/no)
- risk status: high risk or low risk
  - high risk: defined as harboring 17p deletion or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy
  - low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemotherapy or chemoimmunotherapy.
- geographic region (U.S./Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America.

A unique patient number will be assigned at randomization. This patient number will be used to identify the patient in the electronic data capture (EDC) system and all other data sources.

The IDCC and IDMC will be unblinded. Assessments by the IRC will be blinded.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

The Sponsors will be supplying all study treatments for this study (GDC-0199, rituximab, and bendamustine).

4.3.1.1 GDC-0199

GDC-0199 (ABT-199) is manufactured by AbbVie, Inc. and will be supplied as oral tablets of 10 mg, 50 mg, and 100 mg strength. GDC-0199 tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled (either single-panel or booklet) as per individual country requirements. Label must remain affixed to the supplies. GDC-0199 drug must be stored at 15°C – 25°C (59°F – 77°F). The investigational product is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for patient use or returned to the Sponsor.

For further details, see the ABT-199/GDC-0199 Investigator's Brochure.

4.3.1.2 Rituximab

Rituximab is manufactured by Genentech, Inc., as the licensed product Rituxan® in the United States and Canada. For the rest of the world, rituximab is manufactured by F. Hoffmann – La Roche Ltd, Ltd. (Roche) as the licensed product MabThera®. It is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in 100-mg (10-mL) and 500-mg (50-mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with Sterile Water for Injection. The pH is adjusted to 6.5. Vials are for single use. Each vial and carton will be labeled (either single-panel or booklet) as per individual country requirements. Label must remain affixed to the supplies.

Rituximab vials must be stored at 2°C – 8°C (36°F – 46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for infusion may be stored at 2°C – 8°C (36°F – 46°F) for 24 hours and has been shown to be stable for an additional 12 hours at room temperature. However, since rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C – 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

For further details, see the local prescribing information for Rituxan®/MabThera®.

4.3.1.3 Bendamustine

Bendamustine HCl is marketed by Cephalon as the licensed product Treanda® for the United States and is marketed in Germany by Mundipharma International Corporation Ltd, under the name Levact®. Bendamustine will be supplied in individual cartons containing single-use vials of 100 mg bendamustine HCl as lyophilized powder. Bendamustine is formulated for IV administration in either 0.9% sodium chloride injection or 2.5% dextrose/0.45% sodium chloride. Each vial and carton will be labeled (either single-panel or booklet) as per individual country requirements. Label must remain affixed to the supplies.

Bendamustine should be stored at 15°C – 25°C (59°F – 77°F). It is to be retained in the original carton until time of use to protect from light. Bendamustine should be prepared for administration as close as possible to the time of administration. Once diluted with sodium chloride or dextrose/sodium chloride, the final admixture is stable for 24 hours when stored refrigerated (2°C – 8°C or 36°F – 47°F) or for 3 hours when stored at room temperature (15°C – 30°C or 59°F – 86°F) and room light. Administration of bendamustine must be completed within this period.

For further details, see the local prescribing information for Treanda®/Levact®

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 GDC-0199

Following an initial GDC-0199 ramp-up period (see Section 4.3.2.1.1), patients randomized to Arm A (GDC-0199+R) will take GDC-0199 400 mg daily orally in combination with rituximab administered intravenously on Day 1 of each 28-day cycle for 6 cycles. After completion of combination therapy, patients will continue to take GDC-0199 400 mg daily orally as monotherapy until disease progression or for a maximum of 2 years from Cycle 1, Day 1.

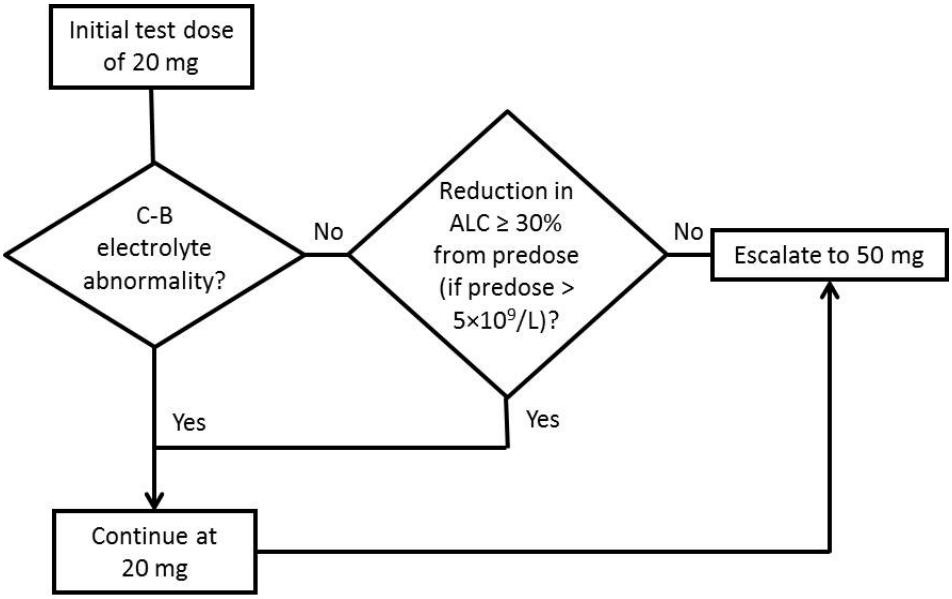
4.3.2.1.1 GDC-0199 Ramp-Up Period

To mitigate potential serious complications of TLS, patients will require close clinical and laboratory monitoring during the GDC-0199 ramp-up period. See Section 4.4.1.2 for details of the TLS prophylaxis and monitoring guidelines.

A test dose of 20 mg of GDC-0199 will be administered orally for all patients on Day 1. If a patient demonstrates one or more electrolyte abnormalities suggestive of laboratory TLS (LTLS; see Appendix 10) during the 24-hour period after the first dose, electrolyte abnormalities will be treated according to the Electrolyte Management Guidelines provided in Appendix 12. Following resolution of electrolyte abnormalities, patients may be instructed to resume self-administration of GDC-0199 at 20 mg/day for an additional 6 days. Patients will then increase the GDC-0199 dose to 50 mg per day and be monitored as described above. If the 50 mg dose is tolerated without electrolyte abnormalities, daily dosing of GDC-0199 at 50 mg per day will continue for Days 2 – 7.

Patients who do not demonstrate evidence of electrolyte abnormalities suggestive of LTLS during the 24 hours following the 20 mg test dose will be escalated to 50 mg GDC-0199 on Day 2 and will be monitored for LTLS over 24 hours. If the 50 mg dose is tolerated, daily dosing of GDC-0199 at 50 mg per day will continue for an additional 6 days. Figure 3 outlines the initial GDC-0199 dose increase. See Appendix 1 for details regarding the laboratory monitoring plan.

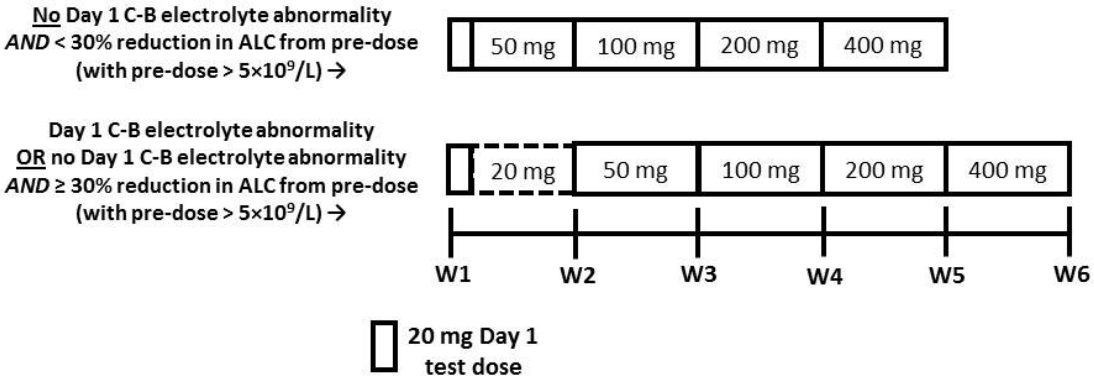
Figure 3 Initial Dose Increase during GDC-0199 Ramp-Up Period



ALC: absolute lymphocyte count; C-B: Cairo – Bishop criteria (see Appendix 10).

GDC-0199 dose increases will continue weekly at 100 mg/day for 1 week, 200 mg/day for 1 week, up to a final dose of 400 mg/day. The duration of the GDC-0199 ramp-up period is expected to be 4 – 5 weeks as shown in Figure 4. Patients will then continue taking GDC-0199 400 mg daily for the duration of the study or as directed by the investigator.

Figure 4 GDC-0199 Dose Ramp-Up Period



ALC: absolute lymphocyte count; C-B: Cairo – Bishop criteria; W: Week.

4.3.2.1.2 GDC-0199 in Combination with Rituximab

After the patient has completed the GDC-0199 ramp-up period and received the target dose of 400 mg of GDC-0199 for 1 week with no evidence of laboratory or clinical TLS, the patient will begin combination therapy consisting of 6 cycles of rituximab (infusions occurring on Day 1 of each 28-day cycle; see Section 4.3.2.2) in combination with the daily dose of GDC-0199. All patients must receive prophylaxis for TLS (Section 4.4.1.2)

prior to the initiation of GDC-0199 and rituximab treatment. Patients at high risk for TLS, or with compromised renal function, may be hospitalized for the first day of Cycle 1 if risk for developing TLS remains high (see Section 4.4.1.2). On days when GDC-0199 and rituximab are given, GDC-0199 will be taken at least 30 minutes prior to starting the rituximab infusion.

Patients will self-administer GDC-0199 tablets by mouth once daily. Each dose of GDC 0199 will be taken with approximately 240 mL of water within 30 minutes after the completion of a low-fat breakfast. Examples of a low-fat breakfast include 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jam, and 8 ounces/240 mL of skim milk (319 calories and 8.2 g fat); or 1 cup/30 g of cereal, 8 ounces/240 mL of skim milk, 1 slice of toast with jam, 1 cup/240 mL of apple juice, and 1 cup/240 mL of coffee or tea (520 calories and 2 g fat). If vomiting occurs within 15 minutes of taking GDC-0199 and all expelled tablets are still intact, another dose may be provided. Otherwise, no replacement dose is to be given. In cases where a dose of GDC-0199 is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken with food within 8 hours of the missed dose. Otherwise, the dose should not be taken.

Patient compliance in taking the assigned daily dose of GDC-0199 will be assessed by standard pill counts. Bottles containing GDC-0199 tablets will be given to patients at regular scheduled visits. Previously distributed bottles will be returned to the clinic and tablets counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Any overdose or incorrect administration of GDC-0199 should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Guidelines for GDC-0199 dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

4.3.2.2 Rituximab

Rituximab will be administered to patients in both treatment arms at 375 mg/m^2 IV on Day 1 of Cycle 1 followed by 500 mg/m^2 on Day 1 of Cycles 2 through 6 (total of six infusions of rituximab).

For patients in Arm A (GDC-0199+R): on days when GDC-0199 and rituximab are given, GDC-0199 will be taken at least 30 minutes prior to starting the rituximab infusion.

For patients in Arm B (BR): on days when rituximab and bendamustine are to be administered, rituximab will be administered prior to bendamustine.

The patient's BSA calculated at screening should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by $>10\%$ from screening. In obese patients, there is no cap on BSA and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥ 30 kg/m^2).

During the treatment period, rituximab must be administered to patients in a clinical (inpatient or outpatient) setting. Rituxan should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur .

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (such as the Braun Infusomat Space) should be used to control the infusion rate of rituximab. Administration sets with polyvinyl chloride (PVC), polyurethane, or polyethylene (PE) as a product contact surface and IV bags with polyolefine, polypropylene, PVC, or PE as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption. Please see Table 1 for instructions regarding first and subsequent infusions of rituximab.

After the end of each dose of rituximab, patients should be observed for 1 hour. If no AEs occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

Rituximab should not be administered as an IV push or bolus. Infusion-related reactions (IRRs) may occur.

Pre-medication consisting of acetaminophen, diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion. Pre-medication may attenuate IRRs. Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

Table 1 Administration of First and Subsequent Infusions of Rituximab

First Infusion (Cycle 1 Day 1)	Subsequent Infusions
Begin infusion at an initial rate of 50 mg/h. If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/h increments every 30 minutes, to a maximum of 400 mg/h. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (ie, 50% of rate being used at the time that the reaction occurred).	If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/h and follow instructions for the first infusion. If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of $\geq$100 mg/h), begin the infusion at a rate of 100 mg/h. If no infusion reaction occurs, increase the infusion rate in 100-mg/h increments every 30 minutes, to a maximum of 400 mg/h. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (ie, 50% of rate being used at the time that the reaction occurred).

Note: A fast infusion is not allowed.

Any overdose or incorrect administration of rituximab should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Guidelines for rituximab dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

4.3.2.3 Bendamustine

Patients randomized to Arm B (BR) will receive bendamustine 70 mg/m^2 administered intravenously on two consecutive days of each 28-day cycle for 6 cycles, in combination with rituximab administered intravenously on Day 1 of each 28-day cycle for 6 cycles (see Section 4.3.2.2 for details of rituximab dosage and administration).

BSA will be calculated at screening and on Day 1 of Cycle 1. The BSA calculated at screening should be used to calculate the dose of bendamustine throughout the study unless the patient's weight increases or decreases by $>$10% from screening. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index$\geq$30 kg/m^2).

Bendamustine will be administered over 60 minutes on Days 1 and 2 of each 28-day cycle for a total of 6 cycles. On days when rituximab and bendamustine are to be administered, rituximab will be administered prior to bendamustine.

Pre-medication with anti-emetics may be administered as per institutional guidelines (see Section 4.4.1). Granulocyte colony-stimulating factor (G-CSF) may be administered as primary prophylaxis in each cycle of therapy, as per the American Society of Clinical Oncology (ASCO) guidelines or each site's institutional standards.

Any overdose or incorrect administration of bendamustine should be noted on the Bendamustine Administration eCRF. AEs associated with an overdose or incorrect administration of bendamustine should be recorded on the AE eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (GDC-0199, rituximab, bendamustine) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to GDC-0199

Currently, the Sponsor does not have any plans to provide GDC-0199 or other study interventions to patients after conclusion of the study (unless required by country-specific regulations) or any earlier patient withdrawal. The Sponsor will evaluate the appropriateness of continuing to provide GDC-0199 to study patients after evaluating the primary efficacy outcome measure and safety data gathered in the study; these analyses may be conducted prior to completion of the study. If these data are medically and statistically significant, the Sponsor may amend the protocol to continue to provide GDC-0199 in an open-label extension study to patients in the treatment arm who have shown a demonstrable benefit from GDC-0199 treatment during this study (as measured by PFS). This open-label extension study would continue until GDC-0199 is commercially available to the participating patients in their countries or until the Sponsor ceases producing or studying GDC-0199.

4.4 CONCOMITANT THERAPY AND FOOD

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (eg, prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 14 days prior to the initiation of study treatment through the end of treatment. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use for the duration of the study or at least one year after the last dose of rituximab, whichever is longer.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (eg, erythropoietin) if clinically indicated. G-CSF may be administered as primary prophylaxis in each cycle of therapy, as per the ASCO guidelines (Smith et al. 2006) or each site's institutional standards.

Antiemetic therapy may be instituted for any patient if clinically indicated. Bendamustine has a moderate risk of emesis (Cheson et al. 2010). It is recommended that bendamustine infusions be administered following premedication with a serotonin (5-HT3) antagonist (ie, dolasteron, ondansetron, etc.) or as per institutional practice.

Systemic steroid therapy will not be allowed either during or within 7 days prior to the first dose of study treatment with the exception of inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease (COPD), single infusions of hydrocortisone prior to rituximab infusions (see Section 4.4.1.1), topical steroids, or replacement corticosteroid therapy for an inherited or acquired deficiency.

4.4.1.1 Premedication before Rituximab

Premedication may attenuate IRRs. The following premedication is required prior to rituximab therapy:

- acetaminophen (650 – 1000 mg) at least 30 minutes prior to the start of all infusions
- diphenhydramine (25 – 50 mg) approximately 30 minutes prior to the start of the first infusion and mandatory for all subsequent infusions unless previous antibody infusions did not result in an IRR > NCI CTCAE Grade 1 and there was no interruption to the infusion. (Another suitable antihistamine is also acceptable and must follow the preceding guidelines.)

A single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered with rituximab if this is the usual practice at the site.

Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

4.4.1.2 Prophylaxis and Management of Tumor Lysis Syndrome

Tumor lysis syndrome is a risk for patients with CLL who are treated with high-cell-killing agents. Clinical data from CLL patients treated to date with GDC-0199 suggest that patients with baseline lymph nodes $\geq$5 cm diameter are at a greater risk for TLS than those with baseline lymph nodes less than 5 cm. In addition, the data showed that creatinine clearance of $\leq$80 mL/min at screening was a secondary risk factor for TLS. A detailed description of risk factors for developing tumor lysis following treatment with GDC-0199 is available in the ABT-199/GDC-0199 Investigator's Brochure. The section below describes the management of patients throughout dosing (as described in Section 4.3.2) based on their risk factors for developing TLS identified upon study entry.

Based on the data review performed by the Sponsors, the following three risk categories for developing TLS were developed:

1. **Low-risk category:** the presence of all measurable lymph nodes with the largest diameter $<$5 cm by radiographic assessment AND absolute lymphocyte counts $<25\times10^9$/L.
2. **Medium-risk category:** the presence of all measurable lymph nodes with the largest diameter $\geq$5 cm and $<$10 cm by radiologic assessment OR absolute lymphocyte count $\geq25\times10^9$/L.
3. **High-risk category:** the presence of any lymph node with the largest diameter $\geq$10 cm by radiologic assessment OR the presence of BOTH an absolute lymphocyte count $\geq25\times10^9$/L AND a measurable lymph node with the largest diameter $\geq$5 cm by radiologic assessment.

All patients enrolling in the study will be assessed at screening and categorized in a risk category as described above. Further details of TLS prophylaxis and monitoring are presented in the following sections.

Initial Dosing

All patients, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to the initiation of the first dose of GDC-0199:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with GDC-0199 and rituximab is completed; rasburicase may be used at the investigator's discretion (0.2 mg/kg as an IV infusion over 30 minutes prior to the first dose of GDC-0199 and subsequently daily for up to 5 days).
- Oral hydration consisting of fluid intake of approximately 3 L/day starting at least 48 hours days prior to the start of treatment.

- Hospitalization for the first GDC-0199 dose of 20 and 50 mg beginning the evening prior to the dose of GDC-0199 and continuing for 24 hours after. Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of 150 to 200 cc/h or as clinically appropriate. Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities prior to the first dose of GDC-0199, or the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- **For patients at high risk for developing TLS**, rasburicase must be administered as prophylaxis at 0.2 mg/kg as an IV infusion over 30 minutes prior to the first dose of GDC-0199 and subsequently daily as needed for up to 5 days. For patients with a contraindication to rasburicase (ie, glucose-6-phosphate dehydrogenase [G6PD] deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in Section 4.5.1.7.

Serial vital signs and TLS laboratory samples will be drawn (serum chemistry as defined in Section 4.5.1.7) prior to the first dose of GDC-0199 and at 4, 6, 8, 10, 12, and 24 hours post-dose; additionally, hematology samples will be drawn at 8 and 24 hours post-dose (see Appendix 1). These samples are to be sent STAT to the laboratory, and the results must be reviewed promptly by the investigator or sub-investigator. Laboratory values obtained prior to the dose of GDC-0199 are to be used to determine whether a patient has developed changes related to TLS and as a baseline for evaluating changes in ALC. GDC-0199 cannot be administered on Day 2 of the GDC-0199 dose ramp-up period until the 24-hour post-dose laboratory values are reviewed.

Following the initial dosing, patients will be monitored to see if they meet any of the following conditions:

1. Evidence of one or more electrolyte abnormalities as defined by Cairo – Bishop criteria (Appendix 10) or clinical TLS.
2. For patients with a pre-dose absolute lymphocyte count $\geq 5 \times 10^9$/L, a reduction in ALC from the pre-dose value greater than 30%.

Patients with evidence of one or more laboratory abnormality as defined by Cairo – Bishop criteria or clinical TLS will have their dose of GDC-0199 held and will undergo aggressive management and further monitoring as per Appendix 12 (Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome) until their laboratory abnormality or clinical symptoms resolve. They will then complete one week with daily dosing of 20 mg GDC-0199. Following the

week of 20 mg of GDC-0199 therapy, patients will receive TLS prophylaxis and hospitalization as described above and escalate to 50 mg of GDC-0199.

Patients with a pre-dose ALC $\geq 5 \times 10^9$/L who experience a reduction in ALC of greater than 30% from baseline (pre-dose) in the absence of electrolyte changes (evidence of one or more laboratory abnormalities as defined by Cairo – Bishop criteria or clinical TLS) will continue daily dosing with 20 mg of GDC-0199 for a week. Following the week of 20 mg of GDC-0199 therapy, patients will receive TLS prophylaxis and hospitalization as described above and escalate to 50 mg of GDC-0199. During hospitalization, serial vital signs and TLS laboratory samples will be drawn (serum chemistry as defined in Section 4.5.1.7) prior to the dose of GDC-0199 and at 4, 6, 8, 10, 12, and 24 hours post-dose; additionally, hematology samples will be drawn at 8 and 24 hours post-dose.

If the laboratory results do not show evidence of one or more laboratory abnormality as defined by Cairo – Bishop criteria or clinical TLS or a reduction in ALC greater than 30% (for patients with a pre-dose ALC $\geq 5 \times 10^9$/L) during the initial 24 hours monitoring after the first 20 mg dose, patients will receive a 50 mg dose on Day 2 and have TLS laboratory samples and vital signs collected at 4, 6, 8, 10, 12, and 24 hours following the first dose of 50 mg; additionally, hematology samples will be drawn at 8 and 24 hours post-dose. The second 50 mg dose of GDC-0199 should not be administered until the Investigator or designee reviews the 24-hour laboratory results following the first 50 mg dose of GDC-0199. Patients may be discharged home if they are asymptomatic and the Investigator deems their condition to be stable.

Patients will also have TLS laboratory parameters and vital signs assessed at 48 hours and 72 hours after the first dose of GDC-0199; these laboratory tests may be performed as an outpatient, but results must be reviewed prior to the patient receiving the next scheduled daily dose of GDC-0199.

Subsequent Dose Increases during the GDC-0199 Ramp-Up Period

Low and Medium Risk

Low- and medium-risk patients are required to be hospitalized only for the initial dose of 20 and 50 mg of GDC-0199. Subsequent dose escalations do not require hospitalization but may be performed at the discretion of the investigator. Dose-escalation visits with hospitalization require collection of vital signs, TLS laboratory samples at pre-dose and 4, 8, 12, and 24 hours post-dose, and hematology samples at pre-dose and 8 and 24 hours post-dose. Dose-escalation visits without hospitalization require collection of serial vital signs and TLS laboratory and hematology samples at pre-dose and 8 and 24 hours post-dose.

High Risk

All high-risk patients are required to be hospitalized for each dose escalation of GDC-0199 and must receive inpatient procedures (IV hydration, nephrology consult, and

serial vital signs and laboratory monitoring) like the first dose. Dose-escalation visits with hospitalization require collection of vital signs, TLS laboratory samples at pre-dose and 4, 8, 12, and 24 hours post-dose, and hematology samples at pre-dose and 8 and 24 hours post-dose. If patients do not develop laboratory or clinical TLS 24 hours after a dose escalation, they can be discharged from the hospital if the investigator feels they are otherwise stable. TLS laboratory values and vital signs for the 24-hour post-dose time point must be reviewed promptly by the investigator or sub-investigator prior to the patient leaving the clinic or receiving any additional study drug. An electrolyte management guideline with detailed intervention steps is provided in Appendix 12 to aid in treatment and prevention of TLS.

Patients classified as high risk for developing TLS who presented at screening with BOTH an absolute lymphocyte count $\geq 25 \times 10^9$/L AND a measurable lymph node with the largest diameter ≥ 5 cm by radiologic assessment may have their TLS risk category reassessed. Prior to dose increases above 50 mg of GDC-199, patients may have a reassessment of their disease status based on their most recent ALC. Based on those results, one of the following two options may be implemented:

- If the patient's ALC decreases to $< 25 \times 10^9$/L, patients may be re-categorized as medium risk and follow the management guidelines for the medium-risk category for the subsequent increases in dose of GDC-0199 during the GDC-0199 dose ramp-up period.
- If the patient's ALC remains $\geq 25 \times 10^9$/L, they will remain in the high-risk category and continue to follow management guidelines for high-risk patients for subsequent dose increases of GDC-0199 during the GDC-0199 dose ramp-up period. Reassessment of the patient's risk category can occur prior to each subsequent dose increase.

Any patient who develops laboratory or clinical TLS meeting Cairo – Bishop criteria must have their GDC-0199 dose held until the electrolyte abnormalities resolve. The patient may resume dosing based on a risk assessment (including tumor burden status), as determined by the investigator.

First Rituximab Dose

For patients determined to be of low or medium risk for TLS:

- The first dose of rituximab may be given as an outpatient.
- TLS laboratory results must be reviewed prior to each dose and at 8 and 24 hours after initiating the rituximab infusion.
- If there is no evidence of TLS 24 hours after rituximab, patients can continue GDC-0199 dosing daily. The 24-hour chemistry values must be reviewed prior to the patient receiving the next day dose of GDC-0199.

- If any laboratory abnormalities consistent with TLS are observed, patients should undergo further management and monitoring as per Appendix 12 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome.

For patients who are at high risk of TLS:

- Patients will be hospitalized for rituximab infusion and for a minimum of 24 hours after initiation of rituximab.
- Hospitalized patients should receive TLS prophylaxis as for initial GDC-0199 dosing, including a uric acid reducer initiated 72 hours prior to infusion and IV hydration.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- Chemistries will be obtained prior to GDC-0199 and rituximab dose, and 4, 8 and 24 hours after initiation of rituximab infusion. Discharge of patient is dependent upon review of the 24-hour laboratory values by the investigator or designee.
- Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring as per Appendix 12, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome.

At the discretion of the investigator, patients categorized as high risk at baseline may undergo reimaging prior to initiation of rituximab. If all nodes are documented to be <10 cm, rituximab may be given as an outpatient. For patients who are deemed to be high risk due to LN ≥ 5 cm and ALC $\geq 25 \times 10^9$/L, if ALC is documented to be $<25 \times 10^9$/L at the time of rituximab infusion, rituximab may be given as an outpatient.

4.4.1.3 Prophylaxis for Infections

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial or *Pneumocystis* infections is permitted. (Although there is a potential for drug–drug interactions, there is likely to be limited potential clinical effects, therefore trimethoprim sulfamethoxazole [Bactrim®] can be considered for *Pneumocystis* prophylaxis with close clinical monitoring.) The Medical Monitor should also be consulted regarding any consideration of the use of azoles as anti-fungal prophylaxis or therapy, because of the potential for drug–drug interactions.

4.4.2 Prohibited Therapy

Patients who require the use of any of the excluded therapies listed below will be discontinued from study treatment.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy

- Radiotherapy
- Immunotherapy
- Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate)
- Any therapies intended for the treatment of leukemia whether FDA-approved or experimental (outside of this study)
- Anti-retroviral medications

Use of warfarin is prohibited during the study.

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or following study treatment until B-cell levels have returned to normal.

Use of the following concomitant medications is prohibited from 7 days prior to initiation of GDC-0199 and during GDC-0199 administration:

- Steroid therapy for anti-neoplastic intent, with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids.
- Strong CYP3A4 inhibitors such as fluconazole, ketoconazole, and clarithromycin.
- Strong CYP3A4 inducers such as rifampin, carbamazepine, phenytoin, and St. John's Wort.

Concomitant medications that fall into the categories below could potentially lead to adverse reaction(s) and should be considered cautionary (except where noted). If a potential study patient is taking any of the medications in the categories described below, the investigator will assess and document the use of medications known or suspected to fall in the following medication categories:

- Moderate/weak CYP3A inducers such as efavirenz and oxcarbazepine.
- CYP2C8 substrates such as thiazolidinediones (glitazones) and select statins (due to expected inhibition of the metabolism of CYP2C8 substrates by GDC-0199).
- CYP2C9 substrates such as tolbutamide (due to expected inhibition of the metabolism of CYP2C9 substrates by GDC-0199). It is recommended to exclude CYP2C9 substrates with a narrow therapeutic index such as phenytoin.
- CYP1A2 inhibitors and inducers because of possible interaction with bendamustine, a CYP1A2 substrate.

A sample list of excluded medications and cautionary medications that fall into the categories within this section can be found in Appendix 9. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, please refer to the appropriate product label.

4.4.3 Prohibited Food

Use of the following foods is prohibited during the study and for at least 3 days prior to initiation of study treatment:

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

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, cancer history (including prior cancer therapies and procedures), smoking history, and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.1.2 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Targeted physical examinations should be limited to systems of primary relevance—that is, cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen).

Changes from baseline abnormalities at subsequent visits should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Height is to be recorded at screening only. Weight is to be recorded in the standing position (if possible); please see Appendix 1.

Body surface area will be calculated by the formula of Mosteller (1987), as follows:

$$\text{BSA } (m^2) = \{[\text{Height (cm)} \times \text{Weight (kg)}] / 3600\}^{1/2}$$

Body surface area calculated at screening should be used to calculate the dose of rituximab and of bendamustine throughout the study unless the patient's weight increases or decreases by $>10\%$ from screening. In obese patients, there is no BSA cap and actual body weight, not adjusted weight is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥ 30 kg/m^2).

4.5.1.3 Vital Signs and ECOG Performance Status

Vital signs will include measurements of temperature, heart rate, and systolic and diastolic blood pressure after the patient has been in a seated position for 5 minutes.

ECOG performance status (see Appendix 7) will be recorded for patients at screening and at subsequent visits as described in the Schedule of Assessments (Appendix 1).

4.5.1.4 Electrocardiogram

Twelve-lead resting ECGs will be obtained at screening and at subsequent visits, as clinically indicated.

Digital ECG recordings must be obtained at each specified time point. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (eg, television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.1.5 Assessment of Left Ventricular Ejection Fraction

Baseline assessment of ejection fraction will be made at screening by either echocardiogram or multi-gated acquisition (MUGA) scan. Subsequent evaluations of LVEF will be made as clinically indicated for patients who develop signs of cardiac compromise. The decision to enroll a patient with significant cardiac disease in the study will be made by the investigator and Medical Monitor.

4.5.1.6 Tumor and Response Evaluations

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator and by the IRC on the basis of physical examinations, imaging studies, laboratory results, and bone marrow examinations, using iwCLL response criteria for CLL (Hallek et al. 2008) (see Appendix 11).

All patients must have clinical response assessments (including targeted physical examination and laboratory examinations) at screening, at interim assessment (within 14 days of Cycle 4, Day 1), after multi-agent therapy (defined as 4 weeks after Day 1 of Cycle 6 or 4 weeks after Day 1 of the last cycle for early termination), and at 2 – 3 months after Day 1 of the last cycle of multi-agent therapy.

All patients must have CT scans (or MRI if CT is contraindicated) of the neck (if clinically indicated), chest, abdomen, and pelvis with IV and oral contrast at screening, interim assessment (within 14 days of Cycle 4, Day 1) and 2 – 3 months after completion of multi-agent therapy (or 4 weeks after Day 1 of the last cycle for early termination). A follow-up scan must also be performed for patients who meet all clinical and laboratory criteria for CR or PR at subsequent assessment time points. The method of imaging should be consistent for each patient at subsequent time points.

Patients who have not progressed after the 6 cycles of multi-agent therapy will then be followed with response assessments every 12 weeks until progression or close of study, whichever occurs first. Assessments will be based on hematological status and targeted physical examination. Additional imaging evaluations should be performed to confirm a suspected change in response status, that is, SD to PR; or PR to CR/CRi. If a patient's response improves to a CR or CRi during further follow-up, BM examination must be performed to confirm the CR.

If at any time during the study, a patient exhibits clinical signs of possible disease progression (ie, increased or de novo enlargement of liver, spleen, or lymph nodes on physical examination) in the absence of laboratory or histopathologic changes meeting the criteria for PD, then additional assessments including imaging studies and/or BM examination (in setting of new cytopenias) must be performed within 2 weeks to confirm or rule out PD.

Imaging evaluation for response assessment may be limited to areas of prior involvement only, if required by local regulatory authorities. Provisions will be made to collect and store all imaging studies for IRC review.

Bone marrow examinations should include aspirate and biopsy for morphology and biomarker studies, and are required at screening, unless the patient has had bone marrow examination within 8 weeks of study start and laboratory results are available. For those patients who have achieved a CR or CRi (including an imaging evaluation indicating a possible CR), a BM aspirate and biopsy will be obtained to confirm the CR 2 – 3 months following the initial clinical assessment of the CR. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. Any additional/unscheduled BM examinations performed during the study will be at the discretion of the investigator. Results of all BM assessments should be forwarded to the Sponsor.

4.5.1.7 Laboratory Assessments

Local Laboratory Assessments

Samples for the following standard laboratory tests will be sent to the study site's local laboratory for analysis:

- 17p deletion by FISH testing (the results will be used to determine 17p deletion status as positive or negative for study enrollment). Results from a prior laboratory test may be used if available.
- Hematology: complete blood count (hemoglobin, hematocrit, red blood cell [RBC] count, white blood cell [WBC] count), platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and percent or absolute differential counts (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- Quantitative immunoglobulins (IgA, IgG, IgM)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and uric acid.
  - Please note that at room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation in samples collected after treatment with rasburicase:
    - Uric acid must be analyzed in plasma.
    - Blood must be collected into pre-chilled tubes containing heparin anticoagulant. **Immediately immerse plasma samples for uric acid measurement in an ice water bath.**
    - Plasma samples must be prepared by centrifugation in a pre-cooled centrifuge (4°C).
    - Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.
- Viral serology and detection:
  - Hepatitis B (HBsAg and HBcAb)
  - Hepatitis C virus antibody (also HCV RNA by PCR if the patient is HCV-antibody-positive)
- Serum pregnancy test (females).
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) .
- Coagulation (INR, aPTT/PTT, PT).

Central Laboratory Assessments

Samples for flow cytometry, PK assessments, and BM assessments will be sent to one or several central laboratories or to Genentech, Inc. for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- CLL prognostic factors, IgVH mutational status, serum β2-microglobulin, *p53* mutation status, and interphase FISH for chromosomal abnormalities, including central confirmation of 17p deletion, 11q deletion, 13q deletion, and trisomy 12.
- Lymphocyte subset counts: whole-blood samples will be analyzed by flow cytometry for B cells (CD19+) and T-cell subsets (CD3+, CD4+, CD8+), and NK cells (CD16+, CD56+).
- Minimal residual disease (MRD): MRD measurements will be performed at a central laboratory by an accepted methodology.
- Blood and BM aspirate for Bcl-2 family expression (including Bcl-2:Bim complex) by RNA and protein.
- Formalin fixed BM biopsy (or other tumor biopsy) for Bcl-2 family expression by immunohistochemistry.
- Peripheral blood for PK analysis, in vitro sensitivity to GDC-0199 and for pharmacogenomics.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.1.8 Patient-Reported Outcomes

Patient-reported outcome data will be elicited from the patients in this study to more fully characterize the clinical profile of GDC-0199. The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient at specified time points during the study. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires on paper (EORTC QLQ-C30, EORTC CLL-16, and EQ-5D) should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment. For the MDASI questionnaire, patients will be contacted by phone and an interactive voice response solution (IVRx) will be used to capture PRO questionnaire data. The data will be transmitted to a centralized database at the IVRx vendor. The data can be accessed by appropriate study personnel securely via the worldwide web.

The M. D. Anderson Symptom Inventory (MDASI; Cleeland et al. 2000) is a cancer-related multi-symptom, valid, and reliable self-report questionnaire for clinical and research use. It consists of 19 items over two scales that assess symptom severity and symptom interference with different aspects of a patient's life. Thirteen items (ie, pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, and numbness or tingling) ask

patients to rate how severe the symptoms were when “at their worst” in the last 24 hours. An additional six items ask patients to rate how much the symptoms have interfered with six areas of function (ie, general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. Additionally, the MDASI contains tumor-specific modules to assess disease-specific symptoms. For this study, to specifically assess CLL symptoms and treatment side-effects, patients will rate six additional symptoms (night sweats, fevers and chills, lymph node swelling, diarrhea, bruising easy or bleeding, and constipation). The MDASI items are rated from 0 to 10, with 0 indicating that the symptom is either not present or does not interfere with the patient’s activities and 10 indicating that the symptom is “as bad as you can imagine” or “interfered completely” with the patient’s life. The MDASI takes approximately 5 minutes to complete. The MDASI assessment will be conducted using IVRx during Cycles 1, 2, and 3 on Days 1, 8, and 15 of the cycle.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a validated and reliable self-report measure (Fayers et al. 1999) consisting of 30 questions incorporated into five functional scales (physical, role, cognitive, emotional, and social scales), three symptom scales (fatigue, pain, nausea, and vomiting scales), and a global health status/global quality-of-life scale. The remaining single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) assess the additional symptoms experienced by patients with cancer and the perceived financial burden of treatment. The EORTC QLQ-CLL16 module is designed for patients with Stage 0 to Stage 4 CLL. It is composed of 16 questions that address five domains of HRQoL important in CLL. There are three multi-item scales on fatigue (two items), treatment side-effects and disease symptoms (eight items), and infection (four items), and two single-item scales on social activities and future health worries. The EORTC QLQ-CLL16 module is specific to CLL and is administered in addition to the core questionnaire (EORTC QLQ-C30). The EORTC QLQ-C30 and QLQ-CLL16 questionnaires take 10 – 15 minutes to complete altogether. The baseline assessment is conducted on Cycle 1, Day 1 and subsequent assessments will be conducted on Day 1 of each subsequent cycle of multi-agent therapy (Cycles 2 – 6), followed by administration at early termination (if applicable), after completion of multi-agent therapy (defined as 4 weeks after Day 1 of Cycle 6), at 12 weeks after Day 1 of the last cycle of multi-agent therapy, and long-term follow up.

The EuroQol 5-Dimension (EQ-5D) questionnaire is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient’s health status. The EQ-5D will be utilized in this study for economic modeling. The EQ-5D questionnaire takes 5 minutes or less to complete, and assessments are made on Day 1 of each treatment cycle at the same time as the EORTC QLQ-C30 and QLQ-CLL16 and at early termination (if applicable), after completion of multi-agent therapy (defined as

4 weeks after Day 1 of Cycle 6), at 12 weeks after Day 1 of the last cycle of multi-agent therapy, and long-term follow-up.

4.5.1.9 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (eg, DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Residual tumor samples from bone marrow aspirate or lymph node biopsy may be submitted at the screening visit for DNA, RNA, or protein extraction.

The following samples will be collected for identification of dynamic (non-inherited) biomarkers and genetic (inherited) biomarkers:

- Whole blood samples for DNA, RNA, or protein extraction will be drawn at the screening visit and at the end of treatment.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (eg, health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from study GO28667 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from study GO28667.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 30 days prior to study treatment initiation, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 30 days prior to initiation of study treatment may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. PRO assessments should be performed prior to the completion of other study assessments.

Please see Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at End of Treatment/Early Termination Visit

Patients who discontinue from the study treatment prior to completion of the assigned regimen will be asked to return to the clinic within 4 weeks after the last dose of study drug for a follow-up visit.

Please see Appendix 1 for the schedule of assessments performed at the end of treatment/early termination visit.

4.5.2.4 Follow-Up Assessments

After the end of treatment/early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.6.

Patients who discontinue treatment for an AE in the absence of disease progression or new anti-CLL therapy should still be followed for progression and survival according to the protocol schedule.

Please see Appendix 1 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Unplanned Visits

Please see Appendix 1 for assessments that are required to be performed in case of an unplanned visit.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance.

4.6.1.1 Discontinuation from Study Drug/Treatment

Patients must discontinue study treatment (GDC-0199, bendamustine, rituximab) if they experience any of the following:

- Pregnancy
- Disease progression

Patients who experience toxicity that can be clearly attributed to any particular study drug treatment may discontinue treatment with the specific agent if the toxicity is not tolerable and mitigating strategies are not available or successful. If toxicity cannot be clearly attributed to a single agent and is considered possibly related to the combination treatment, treatment with multiple agents should be discontinued. Patients who discontinue treatment for reasons other than PD should remain on study and continue to have disease assessments per protocol.

Patients in Arm A must discontinue GDC-0199 permanently if they experience any dose delay of ≥4 weeks after the last dose (see Section 5.1.5, Table 2). Patients who discontinue GDC-0199 for reasons other than disease progression should remain on the study and continue to have disease assessments per protocol. Patients in Arm A who discontinue GDC-0199 for any reason should also discontinue rituximab, although they are to continue evaluation per protocol. Patients in Arm A who discontinue rituximab therapy for toxicity (including anaphylaxis) may continue treatment with single-agent GDC-0199 after a discussion between the investigator and the Medical Monitor.

Patients in Arm B who experience an anaphylactic reaction must discontinue treatment with the offending agent (see Section 5.1.5 for guidelines on discontinuation of rituximab or dose reduction/modification and discontinuation of bendamustine). Patients in Arm B who discontinue rituximab for toxicity may be eligible to continue monotherapy with single-agent bendamustine after a discussion between the investigator and the Medical Monitor.

Patients who discontinue study drug/treatment prematurely will be asked to return to the clinic for an end of treatment/early termination visit (see Section 4.5.2.3) and must undergo follow-up assessments (see Section 4.5.2.4). The primary reason for premature study drug/treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug treatment prematurely will not be replaced.

4.6.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No ongoing study activity (ie, all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Risks Associated with GDC-0199

Phase I experience with GDC-0199 has demonstrated that it is generally well tolerated and toxicities appear to be mostly manageable and/or reversible; however, clinical experience is limited, with 77 patients with CLL/SLL treated with single-agent GDC-0199 (study M12-175) or in combination with rituximab (study M13-365) as of April 30, 2013. Please see the ABT-199/GDC-0199 Investigator's Brochure for more information.

a. Tumor Lysis Syndrome

To date, the principal adverse reaction associated with GDC-0199 in the ongoing single-agent phase I dose-escalation study M12-175 has been TLS (primarily, but not exclusively, related to the first dose), and therefore the study has been modified to implement a ramp-up dosing scheme and rigorous TLS prophylaxis (see Section 4.4.1.2).

Experience from study M12-175 has been used to develop a dosing schedule starting at 20 mg/day that is incrementally increased to the target dose for each cohort. Doses that have been safely administered to date from phase I studies will be used in this study.

Tumor lysis syndrome, including cases leading to clinical sequelae and death, has been observed at a dose of 50 mg GDC-0199, and all patients enrolled in study M12-175 are required to receive hydration and an agent to reduce uric acid as TLS prophylaxis at least 72 hours prior to starting GDC-0199 treatment. Laboratory testing is required after initial dosing to monitor for metabolic changes and will be used to assess the need for more intensive monitoring and treatment of metabolic abnormalities caused by rapid cell lysis. Please see Section 4.3.2.1.1 and Section 4.4.1.2 for GDC-0199 dosing instructions and the TLS prophylaxis and monitoring plans, respectively.

b. Cytopenia

Effects on lymphocyte numbers are expected based on the mechanism of action, and modest reductions in neutrophils have been observed with GDC-0199 therapy in patients. Thrombocytopenia and anemia have been reported with GDC-0199 in the ongoing single-agent phase I dose-escalation Study M12-175 that is being conducted in heavily pretreated CLL patients. In certain cases, the condition was preexisting. In this study, blood counts will be monitored closely throughout treatment (see the Schedule of Assessments, Appendix 1). Growth factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infections. Dose interruptions or reductions will be allowed based on toxicity.

c. Infectious Complications

Infections of various types have occurred in patients in the ongoing single-agent phase I dose-escalation study M12-175. CLL itself is associated with impaired immune function and increased infections, and it is unclear whether or how much the incidence could be increased due to GDC-0199 treatment. Patients in this study will be closely monitored for infections and prompt therapy will be instituted, as necessary. Patients are allowed to receive concomitant prophylactic anti-infective therapy at the investigator's discretion.

d. Effects on Cardiac Function

Nonclinical studies demonstrated decreases in cardiac function of approximately 20% in healthy laboratory animals. No patterns of adverse events indicating changes in cardiac function have been reported in clinical studies to date. However, the number of patients exposed and the duration of exposure is still relatively low. Patients enrolled in this trial

are required to have ECGs and assessments of LVEF at baseline and as clinically indicated afterwards.

e. Effects on Fertility

There is a potential for decreased spermatogenesis. Male patients considering preservation of fertility should bank sperm before treatment with GDC-0199. Long-term effects of GDC-0199 on female reproductive potential are unknown.

f. Drug Interactions

Drug – drug interactions may occur with GDC-0199. Co-administration of GDC-0199 with CYP3A4 inhibitors and strong inducers is prohibited. Co-administration with moderate/weak CYP3A4 inducers, CYP2C8 substrates, and CYP2C9 substrates should be undertaken with caution. Please see Appendix 9 for a list of medications that are to be excluded or used with caution in patients receiving GDC-0199.

5.1.2 Risks Associated with Rituximab Therapy

Please see the prescribing information for rituximab for full information.

a. Infusion-Related Reactions

Patients treated with rituximab are at risk for IRRs. Fatal infusion reactions within 24 hours of rituximab infusion can occur; approximately 80% of fatal reactions occurred with the first infusion. Severe reactions to rituximab typically occurred during the first infusion with time to onset of 30 – 120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

b. Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. With rituximab treatment, acute renal failure, hyperkalemia, hypocalcaemia, hyperuricemia, or hypophosphatemia from tumor lysis, some fatal, can occur within 12 – 24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells ($\geq$25 000/mm^3) or high tumor burden confers a greater risk of TLS. Patients treated with GDC-0199 (Arm A) will receive prophylaxis as described above and in Section 4.3.2.1. Patients randomized to Arm B (BR) who develop evidence of TLS should be treated as clinically indicated.

c. Hepatitis B Reactivation

Hepatitis B reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of rituximab treatment and approximately 1 month after the last dose.

Patients with chronic hepatitis B (HBsAg-positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg-negative and anti-HBc-positive) are at a lower risk for reactivation. In a study of 51 hepatitis B carriers with DLBCL who received rituximab, 12% of patients developed evidence of reactivation (Skrabs et al. 2002).

Screen all patients for HBV infection by measuring HBsAg, anti-HBc, and anti-HBs before initiating treatment with rituximab. For patients who show evidence of prior hepatitis B infection, consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy. Monitor patients with evidence of prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following rituximab therapy. HBV reactivation has been reported up to 24 months following completion of therapy. In patients who develop reactivation of HBV while on rituximab, immediately discontinue rituximab and any concomitant chemotherapy and institute appropriate treatment (see Section 5.1.5 and Table 3). Insufficient data exist regarding the safety of resuming rituximab in patients who develop HBV reactivation.

Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will discontinue study treatment.

d. Progressive Multifocal Leukoencephalopathy

Rare cases of progressive multifocal leukoencephalopathy (PML) have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson et al. 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is extremely rare but should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem-cell transplant. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

e. Cardiac Toxicity

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life-threatening. To evaluate baseline risks, patients will be required to undergo assessments of LVEF prior to enrolling in this study. Clinical evidence of cardiac decompensation will be evaluated and managed by the treating physician. The decision to continue a patient on study after developing clinically significant cardiac decompensation will be made by the investigator and the Medical Monitor.

f. Infection

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, *Varicella* zoster virus, West Nile virus, and hepatitis B and C.

g. Severe Mucocutaneous Reactions

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens – Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.

h. Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In post-marketing reports of rituximab, the mean time to documented gastrointestinal perforation was 6 days (range, 1 – 77 days) in patients with NHL.

5.1.3 Risks Associated with Bendamustine

For bendamustine safety monitoring, please see Section 4.3.2.2.1.1 for monitoring plans and instructions for dose delay and modification of bendamustine. Please see the prescribing information for bendamustine for full information.

a. Myelosuppression

Patients treated with bendamustine are likely to experience myelosuppression. Patients who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The use of myeloid growth factors for the primary and secondary prevention of febrile neutropenia is permitted.

b. Infection

Infection, including pneumonia and sepsis, has been reported. Patients with myelosuppression following treatment with bendamustine are more susceptible to infections. The study physician will treat patients with clinical evidence of infection appropriately. See Section 4.3.2.2.1.1 for monitoring plans and instructions for dose delay and modification of bendamustine.

c. Infusion Reactions

Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus, and rash. In rare instances, severe anaphylaxis and anaphylactoid reactions have occurred.

d. Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in association with bendamustine. Preventive measures include maintaining adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly. Allopurinol may be held on days of bendamustine administration. Patients randomized to Arm B (BR) who develop evidence of TLS should be treated as clinically indicated.

e. Cutaneous Reactions

A number of skin reactions have been reported with bendamustine treatment, including rash, toxic skin reactions, and bullous exanthema. In a study of bendamustine in combination with rituximab, one case of TEN occurred. Toxic epidermal necrolysis has been reported for rituximab. Cases of Stevens – Johnson syndrome and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes.

f. Long-Term Stem-Cell Toxicity

Premalignant and malignant diseases, including MDS, myeloproliferative disorders, AML, and bronchial carcinoma, have developed in patients treated with bendamustine.

g. Extravasation of Bendamustine

Erythema, marked swelling, and pain from bendamustine extravasation have resulted in hospitalization.

h. Transfusion-Associated Graft versus Host Disease

Rare cases of transfusion-associated graft versus host disease have been reported following treatment of low-grade B-cell malignancies with purine analogues (ie, fludarabine or cladribine). The situation with newer purine antagonists such as bendamustine is unclear. Transfusions, if required, should be performed according to national guidelines.

i. Drug Interactions

Certain medications may interact with bendamustine. Caution should be used or alternative treatments should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed. Please see Appendix 9 for a list of medications that are to be excluded or used with caution in patients receiving bendamustine.

5.1.4 Risks Associated with GDC-0199 and Rituximab Combination Therapy

Study M13-365 is a phase Ib, open-label, dose-escalation protocol treating patients with first-line and relapsed/refractory CLL and SLL with GDC-0199 and rituximab in combination to determine the maximum tolerated dose and recommended dose of

combination therapy. To date, there is insufficient data from study M13-365 to determine the risk profile of GDC-0199 in combination with rituximab.

5.1.5 Management of Specific Adverse Events

Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

GDC-0199+Rituximab Dosage Modifications

Table 2 Dose Modifications for GDC-0199+Rituximab – Hematologic Toxicity

Hematologic toxicity	
Event(s)	**Dose Delay or Modification**
Grade 3 or 4 neutropenia, without infection or fever, and/or Grade 3 or 4 thrombocytopenia, first episode	• Hold GDC-0199 (and rituximab if neutropenia occurs during Cycles 1-6) • When counts recover to ANC $\geq 1.0 \times 10^9$/L and/or platelets are $\geq 75 \times 10^9$/L resume previous doses of GDC-0199 and rituximab • Administer G-CSF or growth factors for neutropenia as indicated • If patient was not previously receiving prophylactic GCSF, initiate prophylactic G-CSF for current and all subsequent cycles.
Grade 3 or 4 neutropenia with infection and/or fever, first episode	• Hold GDC-0199 (and rituximab if neutropenia occurs drug Cycles 1-6) until fever and/or infection resolves • Administer G-CSF or growth factors for neutropenia as indicated • When counts recover to ANC $\geq 1.0 \times 10^9$/L and infection has been fully treated, resume previous doses of GDC-0199 and rituximab. • If patient not previously receiving prophylactic G-CSF, initiate prophylactic G-CSF for current and all subsequent cycles.
Recurrent Grade 3 or 4 neutropenia with/without fever and infection despite G-CSF	• Hold GDC-0199 (and rituximab if neutropenia occurs during Cycles 1-6) for at least 7 days • Administer G-CSF or growth factors for neutropenia as indicated • When counts recover to ANC $\geq 1.0 \times 10^9$/L and/or platelets are $\geq 75 \times 10^9$/L resume GDC-0199 at one dose level reduction (Table 4) • Reinitiate rituximab at previous dose

Table 2 Dose Modifications for GDC-0199+Rituximab (cont.)

Hematologic toxicity (cont.)	
Event(s)	**Dose Delay or Modification**
Severe thrombocytopenia (platelets < 25 000/μL) and/or symptomatic bleeding	• Hold GDC-0199 (and rituximab if event occurs during Cycles 1-6) for severe thrombocytopenia (platelets < 25 000/μL) or presence of symptomatic bleeding until resolution of bleeding • Platelets may be transfused at the discretion of the investigator • When platelet level rises to > 50 000/μL without transfusional support for 5 consecutive days, restart GDC-0199 and rituximab at previous doses. • For a second episode of severe thrombocytopenia and/or symptomatic bleeding, hold GDC-0199 (and rituximab if event occurs during Cycles 1-6). When platelet level rises to > 50 000 without transfusional support for 5 consecutive days, restart GDC-0199 at one dose level reduction (Table 4). Rituximab may be restarted at the previous dose. • For subsequent episodes of severe thrombocytopenia, hold GDC-0199 (and rituximab if event occurs during Cycles 1-6). When platelet level rises to > 50 000 without transfusional support for 5 consecutive days, restart GDC-0199 at one dose level reduction. Rituximab may be restarted at the previous dose. • For recurrent severe thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, consult the Medical Monitor regarding continuation on protocol.

Table 3 Dose Modifications for GDC-0199+Rituximab – Non-Hematologic Toxicity

Non-hematologic toxicity	
Event(s)	**Dose Delay or Modification**
Grade 4 IRR	Discontinue rituximab permanently. Patients may continue GDC-0199
Grade 3 IRR, first dose	To be managed at investigator's discretion, please note that dose reductions of rituximab are prohibited.
Grade 3 IRR, subsequent episodes	Discontinue rituximab permanently. Patients may continue GDC-0199
Grade 1-2 IRR, first and subsequent episodes	To be managed at investigator's discretion, please note that dose reductions of rituximab are prohibited. Rituximab may be discontinued for patients experiencing recurrent Grade 1-2 IRR.
Grade 3 or 4 tumor lysis syndrome (first episode)	Hold all study treatment (GDC-0199 and rituximab) until TLS resolves. The patient's next dose may be delayed for up to 28 days. Following complete resolution of tumor lysis syndrome, GDC-0199 (and rituximab if event occurs during Cycles 1-6) may be restarted at the previous dose in conjunction with prophylactic hydration and uricosuric agent; hospitalization for restarting the GDC-0199 dose should be considered.
Grade 3 or 4 non-hematologic toxicity not specifically described above	Delay GDC-0199 (and rituximab if event occurs during Cycles 1-6) for a maximum of 28 days. First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of GDC-0199 and rituximab. For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart GDC-0199 at one dose level reduction (Table 4)
Grade 2 non-hematologic toxicity	Delay treatment with GDC-0199 (and rituximab if event occurs during Cycles 1-6) until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. After resolution, resume full dose of GDC-0199 and rituximab.
Grade 1 non-hematologic toxicity	No dose reduction or delay.
Hepatitis B reactivation (as evidenced by new detectable HBV-DNA levels)	HBV-DNA levels between WHO-recommended range of 29 and 100 IU/mL: Re-test within 2 weeks. If still positive, hold GDC-0199, or GDC-0199 and rituximab (if event occurs during Cycles 1-6) and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. HBV-DNA levels at WHO-recommended cutoff of > 100 IU/mL: hold GDC-0199, or GDC-0199 and rituximab (if event occurs during Cycles 1-6) and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. Rising HBV-DNA viral load while on an appropriate anti-viral therapy: Discontinue patient from GDC-0199 and rituximab permanently and refer patient to a gastroenterologist or hepatologist immediately.

Table 4 GDC-0199 Dose Reduction

GDC-0199 Current Dose Level	GDC-0199 Dose Reduction
400 mg	300 mg
300 mg	200 mg
200 mg	Discontinue GDC-0199 and rituximab

Gradual dose increase following resolution of toxicity leading to a dose reduction may be considered if the patient is stable for 2 weeks on the lower dose; however, if the toxicity recurs, the patient may continue treatment on the lower dose.

Patients who discontinue GDC-0199 for toxicity should also discontinue rituximab, although they are to continue evaluation per protocol.

Rituximab Dosage Modifications

There will be no rituximab dose modifications in this study. Patients at high risk for IRRs may, at the investigator's discretion, receive their initial dose of rituximab split over two consecutive days (eg, 125 mg/m^2 on Cycle 1, Day 1 and 250 mg/m^2 on Cycle 1, Day 2).

Rituximab may be temporarily held. Any NCI CTCAE, v4.0 toxicity Grade $\geq$ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment until resolution to Grade $\leq$ 1.

Patients in Arm A (GDC-0199+R) who discontinue rituximab for rituximab-related toxicity may continue to receive GDC-0199. Patients who discontinue GDC-0199 for toxicity should also discontinue rituximab, although they are to continue evaluation per protocol as described in Section 4.6.1.1.

Patients in Arm B (BR) who discontinue rituximab for rituximab-related toxicity may continue to receive bendamustine as a single agent for the full 6 cycles if deemed to be in the best interest of the patient as assessed by the investigator. Patients who discontinue both bendamustine and rituximab are to continue evaluation per protocol as described in Section 4.6.1.1.

Bendamustine Dosage Modifications

Assessment of Hematologic Toxicities

The evaluation of potential treatment-induced toxicity in patients with advanced CLL may be quite difficult and require careful consideration of both the manifestations of the underlying disease, as well as adverse reactions to the therapy under study. Some of the conventional criteria for toxicity are not applicable, especially under circumstances of progressive BM failure from the CLL itself.

Dose modifications for hematologic toxicity in patients with CLL must be made with consideration of the increased frequency of hematologic compromise at the initiation of

therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many patients would be considered to have Grade 2 – 4 hematologic toxicity at presentation.

On the first day of each new treatment cycle and before each bendamustine dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). The following dose-reduction rules for bendamustine should be followed (Table 2 and Table 3):

If toxicities occurred at 70 mg/m^2, reduce dose to 50 mg/m^2; if toxicity occurred at 50 mg/m^2, discontinue bendamustine. If the dose of bendamustine is reduced due to toxicity, it will not be re-escalated later in the study.

Table 5 Bendamustine Dose Reduction

Bendamustine Current Dose Level	Bendamustine Dose Reduction
70 mg/m^2	50 mg/m^2
50 mg/m^2	Discontinue bendamustine

If a patient has disease-related splenomegaly or significant bone marrow involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion

Table 6 Dose Modification Guidelines for Bendamustine

NCI CTCAE category	Severity	Dose Modification
Hematologic[a]	Neutrophil < 1000/μL on Day 1 of Cycles 2 – 6	Initiation (Day 1) of Cycles 2 – 6 should be delayed until the neutrophil count is ≥ 1000/μL (or returns to baseline level obtained at screening) and the platelet count is ≥75 000/μL.[a] If Day 1 is delayed by more than 2 weeks, then bendamustine should be resumed at the next lower dose level.
	Platelets < 75 000/μL on Day 1 of Cycles 2 – 6	
	Grade 4 neutropenia with fever/infection	Initiation (Day 1) of Cycles 2 – 6 should be delayed until the neutrophil count is ≥ 1000/μL without evidence of fever or infection and the platelet count is ≥75 000/μL.[a] Bendamustine should then be resumed at the next lower dose level.
	Grade 4 neutropenia lasting ≥7 days	
	Grade 4 platelets for ≥ 7 days or a platelet count < 10 000/μL at any time	
Nausea, emesis, or diarrhea in the absence of maximal prophylaxis	≥ Grade 3	Continue treatment, but with institution of maximum prophylactic therapy, including a 5-HT_3 antagonist for nausea and emesis, and loperamide, or a comparable antidiarrheal agent, for diarrhea. Events of Grade 4 toxicity require holding treatment until resolution of toxicity to ≤ Grade 2 with use of maximum prophylaxis.
Nausea, emesis, or diarrhea with maximal prophylaxis	≥ Grade 3	Hold bendamustine for up to 2 weeks or until the toxicity returns to ≤ Grade 2, and restart at the next lower dose. If treatment is delayed by more than 2 weeks, treatment with bendamustine must be discontinued.
All other toxicities related to bendamustine	≥ Grade 3	

5-HT3: 5-hydroxytryptamine 3; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

a If patients have disease-related splenomegaly or significant bone marrow involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (ie, the adverse event actually causes or leads to death)
- Life-threatening (ie, the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (ie, the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- Suspected transmission of an infectious agent by the study drug
- Grade > 3 tumor lysis syndrome and infusion-related reaction

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 – 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient’s medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (eg, serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug, or 90 days after last dose of rituximab, whichever is longer. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE, v4.0 will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE, v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (last accessed: April 22, 2013)

a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

c If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

d Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after rituximab and/or bendamustine infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For adverse events other than IRRs, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- if vomiting or diarrhea results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- if vomiting or diarrhea results in severe dehydration, both events should be reported separately on the eCRF.
- if a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- if dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- if neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

In this study, certain abnormal values may not qualify as adverse events. Hematologic parameters should be evaluated as described in Table 2 and Table 3 and in Appendix 12 and Appendix 16. G-CSF used as prophylaxis would not be considered an AE but should be reported as a concomitant medication.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (ie, cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (eg, "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of CLL should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths attributed to progression of CLL should be recorded only on the Survival eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of CLL

Events that are clearly consistent with the expected pattern of progression of the underlying disease (such as transformation to more aggressive histology) should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (ie, inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (eg, for monitoring for potential TLS)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care.

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Paper or electronic questionnaires may be used for this study. In the event paper is used, instructions on the PRO questionnaires will include a disclaimer to let patients know that the site staff will not be reviewing the answers to the questionnaire and therefore patients should alert the site staff about any problems they are having. Site staff will review PRO questionnaires for completeness ONLY. If it is noted that the patient has written any words on the PRO instrument that is not a predefined response (eg, comments in the margin of the questionnaire or comments in an open text field), site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (ie, no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information (North, Latin and South America)

Medical Monitor: [redacted], MD

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor (Roche Medical Responsible) Contact Information (Rest of World)

Medical Monitor: [redacted], MD

Telephone No.: [redacted]

Alternate Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (ie, within 24 hours) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to AbbVie/Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to AbbVie/Roche Safety Risk Management or its designee immediately (ie, no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 days after the last dose of study drug (or within 90 days of the last dose of rituximab). A Pregnancy Report eCRF should be completed by the investigator immediately (ie, no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to AbbVie/Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (eg, an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to AbbVie/Roche Safety Risk Management or its designee immediately (ie, no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after completing treatment with GDC-0199 or 180 days after the last dose of rituximab. Male patients who received study treatment should not attempt to father a child until end of study or for 1 year after the last dose of rituximab. A Pregnancy Report eCRF should be completed by the investigator immediately (ie, no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of

GDC-0199, or 90 days after last dose of rituximab, whichever is longer). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or non-serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug or the female partner of a male patient exposed to study drug.

The investigator should report these events directly to AbbVie/Roche Safety Risk Management via telephone or via fax machine using the Serious Adverse Event Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- ABT-199/GDC-0199 Investigator's Brochure
- Local prescribing information for rituximab
- Local prescribing information for bendamustine

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Details of the analyses presented in this section will be provided in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint of PFS was used to determine the sample size for the study. Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- two-sided log-rank test at the 0.05 level of significance
- 80% power to detect a hazard ratio (HR) for GDC-0199+R versus BR of 0.66, corresponding to an approximate median improvement of 12.3 months to 23 months (34% reduction in risk of a PFS event)
- exponential distribution of PFS
- an annual dropout rate of 5%
- one interim analysis for efficacy, 12 months after the last patient enrolled

With these assumptions, 186 PFS events are required to achieve 80% power for the primary analysis of PFS in all patients. Assuming an enrollment of 20 months, it is planned to enroll 370 patients across two arms, randomized 1:1.

An efficacy interim analysis is planned approximately 12 months after the last patient is enrolled (see Section 6.10). Efficacy will be evaluated at a p value of 0.001 (corresponding to a hazard ratio of approximately 0.59). The minimum detectable difference at the final analysis corresponds approximately to a hazard ratio of 0.75. It is expected that, after a 9-month ramp-up, 24 patients per month will be recruited. Total enrollment is expected to take approximately 20 months.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, eligibility violations, study drug administration, and patient disposition will be summarized by treatment arm in all randomized patients and by 17p deletion status. A summary of patient disposition will include whether treatment was completed or discontinued early and the reason for early treatment discontinuation. Descriptive statistics will be used in evaluating the conduct of the study.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, and baseline ECOG performance status, will be summarized by treatment arm in all randomized patients. Descriptive statistics will be used in evaluating treatment group comparability.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard iwCLL guidelines [Hallek et al. 2008]), or death from any cause, whichever comes first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of the last disease assessment. If no disease assessments were performed after the baseline visit, PFS will be censored at the time of randomization.

The primary analysis of the study will test the equality of PFS distributions for the GDC-0199 and rituximab combination (GDC-0199+R, Arm A) and the bendamustine and rituximab combination (B+R; Arm B), as follows:

$$H_0: PFS_{GDC\text{-}0199+R} = PFS_{BR}$$

versus

$$H_1: PFS_{GDC\text{-}199+R} \neq PFS_{BR}$$

Treatment comparison will be made using a two-sided stratified log-rank test (0.05 significance level, appropriately adjusted for an interim analysis) stratified by 17p deletion status (yes/no), early or late relapse or progression after prior chemotherapy-containing therapy (within 12 months after monotherapy or within 24 months after chemoimmunotherapy versus more than 12 months or 24 months after either), and geographic region (U.S./Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America). If the null hypothesis is rejected and the observed hazard ratio is favorable for the GDC-0199+R combination, then it is shown that GDC-0199+R has significantly longer PFS than BR. The Kaplan – Meier curve will provide a visual description of the differences across treatment arms. Estimates of the treatment effect will be expressed as hazard ratios through use of a stratified Cox proportional-hazards analysis, including 95% confidence intervals.

The following sensitivity analyses for PFS will also be performed:

- An unstratified log-rank test will be performed.
- PFS analyses will be performed with censoring at the initiation of non-protocol-specified anti-lymphoma therapy to assess potential confounding of the treatment effect estimates by subsequent therapy.

Details will be outlined in a Statistical Analysis Plan.

6.4.2 Secondary Efficacy Endpoints

If the study meets its primary endpoint of prolonging PFS assessed by the investigator in the overall study population, then a formal statistical test of PFS as assessed by the IRC between the two arms will be performed at the 0.05 level for the population of patients determined to have 17p deletion. If the study does not meet its primary endpoint, then

this test will not be performed. This fixed-sequence testing of the endpoint of PFS in 17p-deleted patients maintains the type I error level at 0.05 (Alosh and Huque 2010).

Other analyses of secondary endpoints will not be tested formally, and there is no type I error control for these endpoints.

- IRC-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse or death from any cause.
- Investigator-assessed PFS will be analyzed in the subset of CLL patients with 17p deletion identified by central laboratory FISH testing.
- OR (defined as CR+CRi+PR), PR, and CR and CRi 12 weeks after Day 1 of the last cycle of multi-agent therapy as assessed by the investigator. Disease response will be assessed according to the iwCLL guidelines (Hallek et al. 2008).
- OR, PR, CR, and CRi 12 weeks after Day 1 of the last cycle of multi-agent therapy, as determined by the IRC.
- PFS assessed by the investigator and by the IRC.
- OS, defined as the time from randomization to death from any cause.
- DOR, defined for patients with a best OR of CR, CRi, or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse as assessed by the investigator or death from any cause.
- Time to next anti-CLL treatment (TTNT), defined as the time from randomization to start of new non-protocol anti-lymphoma therapy or death from any cause.
- The proportion of patients with MRD-negativity at the disease response assessment time points performed at a central laboratory by ASO-PCR and/or by flow cytometry performed on peripheral blood and/or BM samples.

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients who were not reported as having died at the time of the analysis will be censored at the date when they were last known to be alive as documented by the investigator.

Duration of response is defined for patients with a CR or PR as the time from the date of the initial response (CR or PR) to the date of progression/relapse or death from any cause. For patients achieving a response who have not progressed, relapsed, or died at the time of analysis, DOR will be censored on the date of last disease assessment.

Time to next anti-CLL treatment is defined as the time from the date of randomization to the start date of the next anti-CLL treatment or death from any cause. For patients who have not received the next anti-lymphoma treatment or died at the time of analysis, TTNT will be censored at the date when the patient was last known to be alive without having received additional anti-lymphoma treatment.

Time-to-event endpoints such as OS, DOR, and TTNT will be analyzed using the same statistical methods described for the primary analysis of PFS.

Response rates in the treatment groups will be compared using stratified Cochran – Mantel – Haenszel (CMH) tests. Stratification factors are identical to those used for the primary endpoint. Rates and 95% confidence intervals will be reported for each treatment group.

6.5 SAFETY ANALYSES

Safety endpoints include adverse events, serious adverse events, and adverse events of special interest. The safety analyses will include all randomized patients who received at least one dose of study treatment (GDC-0199, rituximab, or bendamustine), with patients grouped according to the treatment actually received.

Treatment exposure will be summarized, including the number of cycles received by each patient, and the cumulative dose will be summarized by treatment arm.

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. All AEs occurring during or after the first treatment will be summarized by treatment arm and NCI CTCAE grade. In addition, all SAEs will be summarized.

Deaths reported during the study treatment period and those reported after treatment completion/discontinuation will be summarized by treatment arm.

Adverse events leading to early treatment discontinuation and early study withdrawal will be summarized by arm and reason.

Laboratory data with values outside of the normal ranges will be identified. Additionally, select laboratory data will be summarized by treatment arm and grade using the NCI CTCAE. Of note, abnormal laboratory data that are clinically significant will be reported as AEs and summarized in the AE tables.

Vital signs and other physical findings will be summarized by treatment arm.

6.6 PHARMACODYNAMIC ANALYSES

The pharmacodynamics endpoint in this study is serial assessment of B- and T-cell lymphocyte subsets by flow cytometry.

The exploratory pharmacodynamic biomarker analyses will include patients with at least one pre-dose and/or one post-dose biomarker assessment, with patients grouped according to the treatment actually received.

Blood samples for biomarker assessments will be assayed using analytically qualified methods (eg, immunohistochemistry, ELISA, quantitative real-time polymerase chain reaction, and fluorescence-activated cell sorting).

6.7 PHARMACOKINETIC ANALYSES

The PK endpoint in this study is apparent clearance, apparent volume of distribution, and other appropriate PK parameters of GDC-0199.

Population PK methods will be used to characterize the PK of GDC-0199 in this study in conjunction with appropriate historical data. Potential correlations of exposure with dose, demographics, pharmacodynamic variables, safety, and efficacy outcomes may be explored as warranted by the data. The results from the population PK analysis may be reported separately from the Clinical Study Report.

6.8 PATIENT-REPORTED OUTCOME ANALYSES

The PRO endpoints in this study are:

- To compare interference and tolerability of treatment-related symptoms in patients treated with GDC-0199+R versus BR using the MDASI questionnaire.
- To evaluate changes from baseline disease-related symptom scores using the MDASI and EORTC QLQ-C30 and QLQ-CLL16 questionnaires.
- To evaluate time to disease-related symptom progression using EORTC QLQ-C30 and QLQ-CLL16.
- To evaluate interference of treatment and disease-related symptoms on QoL using the MDASI questionnaire.

Scoring for the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 questionnaires will be based on their corresponding user manuals (Fayers et al. 1999, Cleeland 2010). For the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales with more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

Summary statistics of the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales and their changes from baseline will be calculated at each assessment time point for both study arms. Analysis details of these patient-reported outcomes will be provided in the Statistical Analysis Plan.

Disease-related symptom progression will be measured by EORTC QLQ-C30 and EORTC QLQ-CLL questionnaires. Time-to-event Kaplan – Meier analysis on CLL symptoms will be used to demonstrate the time from first treatment to worsening in disease-related symptoms. An event is a change in symptom score by 10 points or more as defined as being clinically important.

6.9 HEALTH ECONOMIC ANALYSIS

Health economic data, as assessed by the EQ-5D, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D assessment that generate a score. Scores at baseline and change from baseline scores for each time point will be quantified using descriptive statistics.

The results from the health economic data analysis may be reported separately from the Clinical Study Report.

6.10 EXPLORATORY ANALYSES

Relationship between various baseline markers and clinical outcome parameters in patients from both arms of the study (including CLL prognostic markers, pro- and anti-apoptotic RNAs and proteins in CLL cells, and pharmacogenomics variables) will be assessed using appropriate laboratory measures.

6.11 INTERIM ANALYSES

The IDMC will evaluate efficacy and safety at one formal interim analysis of investigator-assessed PFS and recommend if the study should be stopped early for efficacy. Summaries and analyses will be prepared by the IDCC and presented by treatment arm for the IDMC's review (see Section 3.1.3).

One interim analysis for efficacy of the primary endpoint of investigator-assessed PFS is planned. The interim analysis will be conducted 12 months after the last patient has been enrolled. Testing for efficacy at the interim analysis will occur at two-sided p value of 0.001. If the p value of the two-sided log-rank test is less than 0.001, the trial will have met its primary efficacy endpoint (corresponding to an observed hazard ratio of approximately 0.60 or better). Note that the interim analysis for efficacy is not based on fixed information fraction. If the total number of investigator-assessed PFS events across both arms exceeds 160 (approximately 86% information) or more at the time of the planned interim analysis, then the interim analysis will not be performed, and only the final analysis will be conducted.

The boundary for efficacy will be p value of 0.001. The final analysis will be performed after 186 events have occurred. The level will be adjusted to incorporate the alpha spent at the interim analysis, so that the overall two-sided type I error rate will be maintained at the 0.05 level.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply electronic eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC

using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data and any other electronic data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

Electronic CRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

Electronic patient-reported outcome (ePRO) data will be collected using an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The ePRO device data are available for view access only via secure access. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic CRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. Electronic CRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an ePRO device to capture PRO data. The data will be transmitted via internet automatically after entry to a centralized database at the ePRO vendor. The data can be reviewed by site staff via secure access to an internet server.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (ie, source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (ie, no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (ie, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in

accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or

authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the US Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol

amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

Approximately 150 international centers will participate in this study to enroll up to approximately 370 patients. Data will be recorded via an electronic data capture (EDC) system from [redacted]) using electronic Case Report Forms (eCRFs; see Section 6.6). Central laboratories will be used for the analyses of and/or management of pharmacodynamic, genotyping, and tissue samples. An interactive voice response system (IxRS) will be used for patient registration, patient number, and dose assignment.

This trial is being conducted globally under a collaboration agreement between F. Hoffmann – La Roche, Ltd. and AbbVie, Inc. F. Hoffmann – La Roche, Ltd. and AbbVie, Inc. will act as co-sponsors of the trial in the United States. AbbVie GmbH & Co. KG (Germany) will act as the sponsor of the trial for participating countries in the European Union. In countries where an AbbVie entity is the sole sponsor, Genentech and a contract research organization will manage the study and carry out certain sponsor responsibilities delegated to Genentech by AbbVie, in accordance with applicable laws/regulatory requirements.

AbbVie, Inc., is the holder of the U.S. IND under which this study is being conducted. AbbVie will file all clinical trial applications for this study outside of the United States.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Patients Randomized to Arm A (GDC-0199+R)

Arm A (GDC-0199+R)	Screening	GDC-0199 Ramp-up Period						Multi-agent (GDC-0199+R) Therapy							GDC-0199 Monotherapy			
								Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	22	(28)[u]	1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 mos (earliest 2 mos) after Day 1 of last cycle of multi-agent therapy	every 12 wks after 3-month post-multi-agent FU until 3 yrs then every 6 mos until 5 yrs
Visit Window (±days)	Day -28 to -1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	± 1	within 14 days of C4D1	±7	±7	±7	±7
Informed consent	X																	
Demographic data [a]	X																	
General medical history and baseline conditions	X																	
Concomitant medications, adverse events and compliance assessment	X	X	X	X		X	(X)	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X						X				X			X	X	X	X

Appendix 1
Schedule of Assessments (cont.)

Arm A (GDC-0199+R)	Screening	GDC-0199 Ramp-up Period						Multi-agent (GDC-0199+R) Therapy							GDC-0199 Monotherapy			
								Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	22	(28)[u]	1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 mos (earliest 2 mos) after Day 1 of last cycle of multi-agent therapy	every 12 wks after 3-month post-multi-agent FU until 3 yrs then every 6 mos until 5 yrs
Visit Window (±days)	Day -28 to -1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	± 1	within 14 days of C4D1	±7	±7	±7	±7
Vital signs [b]	X	X[b]	X[b]	X[b]	X[b]	X[b]	(X)[b]	X	X	X	X	X	X		X	X	X	X
Height (at screening only), weight, calculation of BSA	X							X		X	X	X			X	X	X	X
Physical examination [c]	X																	
Targeted physical examination		X	X	X	X	X	(X)	X		X	X	X			X	X	X	X
Assessment of LVEF [d]	X														X	X		
CLL response assessment [e]	X													X	X	X	X	X

Appendix 1
Schedule of Assessments (cont.)

Arm A (GDC-0199+R)	Screening	GDC-0199 Ramp-up Period						Multi-agent (GDC-0199+R) Therapy							GDC-0199 Monotherapy			
								Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	22	(28)[u]	1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 mos (earliest 2 mos) after Day 1 of last cycle of multi-agent therapy	every 12 wks after 3-month post-multi-agent FU until 3 yrs then every 6 mos until 5 yrs
Visit Window (±days)	Day -28 to -1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	± 1	within 14 days of C4D1	±7	±7	±7	±7
CT (or MRI) scan [e]	X													X[e]	X[e]		X[e]	(X)
Bone marrow aspirate and biopsy (including flow cytometry or IHC) [f]	X														(X)	(X)	(X)	(X)
Pregnancy test [g]	X																	
Viral serologies [h]	X																	
Hospitalization [i]		X	X	(X)	(X)	(X)	(X)	(X)										
Hematology [j]	X	X[l]	X[l]	X[l]	X[l]	X[l]	(X)[l]	X[l]	X	X	X	X	X		X	X	X	X
Coagulation	X																	

Appendix 1
Schedule of Assessments (cont.)

Arm A (GDC-0199+R)	Screening	GDC-0199 Ramp-up Period						Multi-agent (GDC-0199+R) Therapy							GDC-0199 Monotherapy			
								Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	22	(28)[u]	1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 mos (earliest 2 mos) after Day 1 of last cycle of multi-agent therapy	every 12 wks after 3-month post-multi-agent FU until 3 yrs then every 6 mos until 5 yrs
Visit Window (±days)	Day -28 to -1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	± 1	within 14 days of C4D1	±7	±7	±7	±7
Serum chemistry [k]	X	X[l]	X[l]	X[l]	X[l]	X[l]	(X)[l]	X[l]	X	X	X	X	X		X	X	X	X
B-, T- and NK-cell markers (flow cytometry) [m]	X													X	X	X	X	X
Urinalysis [n]	X																	
Serum QIG [o]	X													X	X	X	X	X
CLL prognostic factors (including CLL FISH for 17p) [p]	X																	

Appendix 1
Schedule of Assessments (cont.)

Arm A (GDC-0199+R)	Screening	GDC-0199 Ramp-up Period						Multi-agent (GDC-0199+R) Therapy							GDC-0199 Monotherapy			
								Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	22	(28)[u]	1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 mos (earliest 2 mos) after Day 1 of last cycle of multi-agent therapy	every 12 wks after 3-month post-multi-agent FU until 3 yrs then every 6 mos until 5 yrs
Visit Window (±days)	Day -28 to -1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	± 1	within 14 days of C4D1	±7	±7	±7	±7
MRD on peripheral blood [q]	X													X	X	X	X	X[q]
Blood and bone marrow samples for Bcl-2 family (RNA, flow cytometry) [r]	X														X			

Appendix 1
Schedule of Assessments (cont.)

Arm A (GDC-0199+R)	Screening	GDC-0199 Ramp-up Period						Multi-agent (GDC-0199+R) Therapy							GDC-0199 Monotherapy			
								Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	22	(28)[u]	1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 mos (earliest 2 mos) after Day 1 of last cycle of multi-agent therapy	every 12 wks after 3-month post-multi-agent FU until 3 yrs then every 6 mos until 5 yrs
Visit Window (±days)	Day -28 to -1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	± 1	within 14 days of C4D1	±7	±7	±7	±7
Blood sample for in vitro sensitivity to GDC-0199 [r]	X																	
Blood sample for Bcl-2: Bim analysis [r]	X																	
Tumor cells for Bcl-2 family by IHC (formalin fixed tissue) [s]	X																	
Optional Roche Clinical Repository samples[t]	X														X	X		

Appendix 1
Schedule of Assessments (cont.)

Arm A (GDC-0199+R)	Screening	GDC-0199 Ramp-up Period						Multi-agent (GDC-0199+R) Therapy							GDC-0199 Monotherapy			
								Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	22	(28)[u]	1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 mos (earliest 2 mos) after Day 1 of last cycle of multi-agent therapy	every 12 wks after 3-month post-multi-agent FU until 3 yrs then every 6 mos until 5 yrs
Visit Window (±days)	Day -28 to -1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	± 1	within 14 days of C4D1	±7	±7	±7	±7
GDC-0199 [u]		X	X	X	X	X	(X)	X	X	X	X	X	X	X	X	X	X	X
Rituximab [v]								X	X			X						
MDASI [w]								X		X	X	X						
EORTC QLQ-30 and CLL-16 [x]								X				X			X	X	X	X
EQ-5D [x]								X				X			X	X	X	X
ECG [y]	X																	
PK sampling [z]								X										

Appendix 1
Schedule of Assessments (cont.)

BSA: body surface area; C4D1: Cycle 4, Day 1; CLL: chronic lymphocytic leukemia; CR: complete response; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ C-30/CLL16: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30/ Chronic Lymphocytic Leukemia Module 16 questionnaires; EQ-5D = EuroQol's EQ-5D questionnaire; FISH: fluorescence in situ hybridization; HBcAb: serum immunoglobulin G antibody directed at hepatitis B core antigen; HBsAg: hepatitis B virus surface antigen; IgG anti-Hep C Ab: serum ant body directed against hepatitis C virus; IHC: immunohistochemistry, IV: intravenous; LVEF: left ventricular ejection fraction; MDASI = M. D. Anderson Symptom Inventory; MRD: minimal residual disease; MRI: magnetic resonance imaging; NK: natural killer cell; PK: pharmacokinetic; PO: per os, orally; PRO: patient-reported outcome; QIG: quantitative immunoglobulin (including serum levels of IgA, IgG and IgM); R: rituximab; TLS: tumor lysis syndrome.

a Subject age, sex, race, self-reported ethnicity.

b Vital signs will include measurements of temperature, heart rate, systolic and diastolic blood pressure. Vital signs should be collected at all times of chemistry blood draws.

c Complete physical examination is required at screening; targeted physical examination for all subsequent visits. Complete physical examination includes all systems of the body as described in the body of the protocol. Targeted physical examinations should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymphatics (including spleen), and gastrointestinal (including liver), and those associated with clinical signs/symptoms).

d Assessment of LVEF by either echocardiogram or multigated acquisition (MUGA) scan after screening is at the discretion of the investigator.

e All patients must have clinical response assessments (including targeted physical examination and laboratory examinations) at screening, at interim assessment (within 14 days of Cycle 4, Day 1), and 4 weeks after Day 1 of the last cycle. All patients must have a baseline CT scan (or MRI if CT is contraindicated) of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. A follow-up scan must also be performed within 14 days of Cycle 4, Day 1 visit and following completion of multi-agent therapy or early termination (2-3 months after Day 1 of the last cycle). Targeted physical examination and laboratory examinations should be repeated to confirm that patients are still in response prior to confirmatory CT or MRI scan. Imaging evaluations at subsequent study visits are only required to confirm a new response or progressive disease. Imaging evaluations must be performed within 2 weeks for patients who meet the clinical criteria for PD (ie, increased or de novo enlargement of liver, spleen, or lymph nodes on physical examination) in the absence of laboratory or histopathologic criteria for PD. MRI scans of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used instead of CT scans in patients for whom CT scans with contrast are contraindicated (ie, patients with contrast allergy or impaired renal clearance). Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis. If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study.

f A bone marrow examination must be performed at screening unless a bone marrow examination has been performed within 8 weeks prior to Day 1 and laboratory results are available. For those patients who have achieved a CR or cytopenic CR (including a CT scan indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR at least 8 weeks following the initial clinical assessment of CR. A bone marrow aspirate should be obtained for MRD assessment to confirm a molecular CR. Bone marrow examination should be performed as needed within 2 weeks for patients who show clinical suspicion for PD (ie, increased or de novo enlargement of liver, spleen, or lymph nodes on physical exam) in the absence of laboratory or histopathologic criteria for PD. Any additional/unscheduled bone marrow examinations performed during the study will be at the discretion of the investigator.

g Required for all women of reproductive potential (see inclusion criteria).

h HBsAg, IgG anti-HBcAb, and Hep C Ab serology (also HCV, and RNA by polymerase chain reaction if the patient is HCV antibody positive) required.

Appendix 1
Schedule of Assessments (cont.)

i Refer to Section 4.4.1.2 for hospitalization and prophylaxis measures for TLS.

j Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count), platelet count, absolute neutrophil count, absolute lymphocyte count, and percent or absolute differential counts (eg, segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells). At baseline and all subsequent evaluations, cytopenias are to be graded per the National Cancer Institute Working Group Guidelines (see Appendix 18). All scheduled blood draws may be drawn up to 72 hours prior to the next planned evaluation.

k Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), a kaline phosphatase, lactate dehydrogenase, and uric acid. All scheduled blood draws may be drawn up to 72 hours prior to the next planned evaluation.

l Serum chemistries (described in Appendix 1, footnote k) should be drawn at the specific time points as described in detail in Section 4.4.1.2.

m Peripheral blood lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16, and CD56) measured by flow cytometry are required at screening, interim assessment (within 14 days of Cycle 4, Day 1), early termination or end of treatment, 12 weeks after Day 1 of the last cycle of multi-agent therapy, and every 12 weeks thereafter.

n Consists of specific gravity, pH, blood, protein, glucose, ketones, and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

o QIG: quantitative immunoglobulin (including serum levels of IgA, IgG and IgM).

p Patients will have the following samples drawn at screening: serum for β2-microglobulin, whole blood for IgV_H mutational status, *p53* and other prognostic mutations, and interphase FISH for chromosomal abnormalities including 17p-, 11q-, 13q-, and trisomy +12. Sample will be taken for both local and central testing of 17p deletion by FISH

q MRD samples collected at baseline, within 14 days of C4D1 (interim assessment), end of treatment/early termination visit, and at 3, 6, and 12 months after completion of combination therapy will be measured at a central laboratory.

r Whole blood predictive biomarker sample is required for all patients at screening and at time of progression (early termination if applicable) or at end of treatment, one tube each for protein and RNA analysis of Bcl-2 family members. A predictive bone marrow aspirate sample (1 mL each for protein and RNA analysis) must be drawn for all patients at screening. For those patients for whom have a bone marrow examination has been performed within 8 weeks prior to Cycle 1, Day 1 and therefore do not need a bone marrow aspirate draw at screening, are not required to provide a predictive bone marrow aspirate sample. Aspirate samples should be split from samples obtained for International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute Working Group or International Working Group criteria assessment whenever poss ble. If aspirate sample is limiting, then protein should be prioritized over RNA sample. Please note that a bone marrow biopsy and aspirate is not required at the time of progression (unless it is needed to confirm or rule out PD); however, if it is performed then a predictive bone marrow biomarker sample should also be drawn. Predictive biomarker sample will be used for assessment of Bcl-2 family and other relevant markers by RNA and flow in the blood and bone marrow. Additional biomarker assessments will include a blood sample which will be collected at Cycle 1, Day1 pre-dose and 4-hours post-dose for Bcl-2:Bim complex by protein in blood; a blood sample collected at screening for GDC-0199 in vitro sensitivity.

s If formalin fixed specimen of bone marrow biopsy (also including lymph node or other biopsies) is collected at screening by the site as per standard clinical assessment of the patient, a sample should be provided for IHC analysis of Bcl-2 family.

t Residual tumor specimens are requested at screening and optional blood samples are requested at screening and at the end of multi-agent therapy or end of treatment/early termination visit for collection and storage at the Roche Clinical Repository.

Appendix 1
Schedule of Assessments (cont.)

u For patients randomized to Arm A, GDC-0199 will be taken daily by mouth starting on Day 1 through the end of study. As described in Section 4.3.2.1, there will be a 4 to 5 week GDC-0199 ramp-up period when patients will start with a 20 mg dose on Day 1. Depending on how they respond to the first dose, patients may increase to 50 mg on Day 2 or Day 8 and subsequently increase the dose weekly. To reach the dose of 400 mg for the study, it can therefore take 4 to 5 weeks (4 weeks if they have a week of 20/50, 100, 200 and 400 mg; 5 weeks if they have a week of 20, 50, 100, 200, and 400 mg). Patients will continue GDC-0199 at 400 mg PO daily with concurrent rituximab for 6 cycles of 28 days each. Patient with no evidence of progression will continue single agent GDC-0199 (400 mg PO daily) until progressive disease, unacceptable toxicity, or for a maximum of 2 years.

v On Day 1 of Cycle 1, patients will receive rituximab 375 mg/m^2 IV followed by rituximab 500 mg/m^2 IV on Day 1 of Cycles 2 through 6. Investigators will have the option of administering the rituximab dose for Day 1 Cycle 1 over 2 days (eg, 100 mg IV on Day 1, Cycle 1 followed by the remainder of the 375 mg/m^2 dose on Day 2, Cycle 1).

w The MDASI questionnaire will be completed at home on the specified days. The patients will be contacted by phone and an interactive voice response solution (IVRx) will be used to capture the MDASI questionnaire data.

x Patients should complete the questionnaires prior to study drug administration and any other study assessments. PRO assessments should be performed prior to progression, at the time of progression, and at the first assessment after progression.

y An ECG is required at screening only as clinically indicated.

z PK data will be collected for patients randomized to Arm A only. Unscheduled PK sample will be collected from patients developing laboratory or clinical evidence of TLS. PK samples are to be collected on Day 1 of Cycle 1 and on Day 1 of Cycle 4 at the time points descr bed in Appendix 2.

Appendix 1
Schedule of Assessments (cont.)

Patients Randomized to Arm B (BR)

Arm B (BR)	Screening	Multi-agent (BR) Therapy							Observation and Follow-up			
		Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post-Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 months (earliest 2 months) after Day 1 of last cycle of multi-agent therapy	every 12 weeks after 3-month post-multi-agent FU until 3 years then every 6 months until 5 years
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	within 14 days of C4D1	±7	±7	±7	±7
Informed consent	X											
Demographic data [a]	X											
General medical history and baseline conditions	X											
Concomitant medications, adverse events and compliance assessment	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X				X			X	X	X	X
Vital signs[b]	X	X	X	X	X	X	X		X	X	X	X

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Multi-agent (BR) Therapy							Observation and Follow-up			
		Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post-Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 months (earliest 2 months) after Day 1 of last cycle of multi-agent therapy	every 12 weeks after 3-month post-multi-agent FU until 3 years then every 6 months until 5 years
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	within 14 days of C4D1	±7	±7	±7	±7
Height (at screening only), weight and calculation of BSA	X	X		X	X	X			X	X	X	X
Physical examination [c]	X											
Targeted physical examination		X		X	X	X			X	X	X	X
Assessment of LVEF	X											
CLL response assessment [d]	X							X	X	X	X	X
CT (or MRI) scan [d]	X							X[d]	X[d]		X[d]	(X)[d]

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Multi-agent (BR) Therapy							Observation and Follow-up			
		Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post-Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 months (earliest 2 months) after Day 1 of last cycle of multi-agent therapy	every 12 weeks after 3-month post-multi-agent FU until 3 years then every 6 months until 5 years
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	within 14 days of C4D1	±7	±7	±7	±7
Bone marrow aspirate and biopsy (including flow cytometry or IHC) [e]	X								(X)[e]	(X)[e]	(X)[e]	(X)[e]
Pregnancy test [f]	X											
Viral serologies [g]	X											
Hematology [h]	X	X	X	X	X	X	X		X	X	X	X
Coagulation	X											
Serum chemistry [i]	X	X	X	X	X	X	X		X	X	X	X
B-, T- and NK-cell markers (flow cytometry) [j]	X							X	X	X	X	X
Urinalysis [k]	X											

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Multi-agent (BR) Therapy							Observation and Follow-up			
		Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post-Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 months (earliest 2 months) after Day 1 of last cycle of multi-agent therapy	every 12 weeks after 3-month post-multi-agent FU until 3 years then every 6 months until 5 years
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	within 14 days of C4D1	±7	±7	±7	±7
Serum QIG	X							X	X	X	X	X
CLL prognostic factors (including CLL FISH for 17p) [l]	X											
MRD on peripheral blood [m]	X							X	X	X	X	X[m]
Blood and bone marrow samples for Bcl-2 family (RNA, flow cytometry) [n]	X								X			
Tumor cells for Bcl-2 family by IHC (formalin fixed tissue) [o]	X											
Optional Roche Clinical Repository samples [p]	X								X	X		

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Multi-agent (BR) Therapy							Observation and Follow-up			
		Cycle 1				Cycles 2-6			Early Termination (if applicable)	Completion of Multi-agent Therapy	3-month post-Multi-agent Follow-up	Follow-up Visits
Day		1	2	8	15	1	2	Interim Assessment	4 weeks after Day 1 of last dose of study drug	C6D1 +4 weeks	3 months (earliest 2 months) after Day 1 of last cycle of multi-agent therapy	every 12 weeks after 3-month post-multi-agent FU until 3 years then every 6 months until 5 years
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	within 14 days of C4D1	±7	±7	±7	±7
Rituximab [q]		X	X			X						
Bendamustine [r]		X	X			X	X					
MDASI [s]		X		X	X	X						
EORTC QLQ-30 and CLL-16 [t]		X				X			X	X	X	X
EQ-5D [t]		X				X			X	X	X	X
ECG [u]	X											

BSA: body surface area; C4D1: Cycle 4, Day 1; CLL: chronic lymphocytic leukemia; CR: complete response; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ C-30/CLL16: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30/ Chronic Lymphocytic Leukemia Module 16 questionnaires; EQ-5D = EuroQol's EQ-5D questionnaire; FISH: fluorescence in situ hybridization; HBcAb: serum immunoglobulin G antibody directed at hepatitis B core antigen; HBsAg: hepatitis B virus surface antigen; IgG anti-Hep C Ab: serum ant body directed against hepatitis C virus; IHC: immunohistochemistry, IV: intravenous; LVEF: left ventricular ejection fraction; MDASI = M. D. Anderson Symptom Inventory; MRD: minimal residual disease; MRI: magnetic resonance imaging; NK: natural killer cell; PK: pharmacokinetic; PO: per os, orally; PRO: patient-reported outcome; QIG: quantitative immunoglobulin (including serum levels of IgA, IgG and IgM); R: rituximab; TLS: tumor lysis syndrome.

Appendix 1
Schedule of Assessments (cont.)

a Subject age, sex, race, self-reported ethnicity.

b Vital signs will include measurements of temperature, heart rate, systolic and diastolic blood pressure.

c Complete physical examination is required at screening; targeted physical examination for all subsequent visits. Complete physical examination includes all systems of the body as described in the body of the protocol. Targeted physical examinations should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymphatics (including spleen), and gastrointestinal (including liver), and those associated with clinical signs/symptoms).

d All patients must have clinical response assessments (including targeted physical examination and laboratory examinations) at screening, at interim assessment (within 14 days of Cycle 4, Day 1), and 4 weeks after Day 1 of the last cycle. All patients must have a baseline CT scan (or MRI if CT is contraindicated) of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. A follow-up scan must also be performed for patients who meet all clinical and laboratory criteria for CR or PR within 14 days of Cycle 4, Day 1 and following completion of multi-agent therapy or early termination (2-3 months after Day 1 of the last cycle). Targeted physical examination and laboratory examinations should be repeated to confirm that patients are still in response prior to confirmatory CT or MRI scan. Imaging evaluations at subsequent study visits are only required to confirm a new CR. Imaging evaluations must be performed within 2 weeks for patients who meet the clinical criteria for PD (ie, increased or de novo enlargement of liver, spleen, or lymph nodes on physical examination) in the absence of laboratory or histopathologic criteria for PD. MRI scans of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used instead of CT scans in patients for whom CT scans with contrast are contraindicated (ie, patients with contrast allergy or impaired renal clearance). Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis. If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study.

e A bone marrow examination must be performed at screening unless a bone marrow examination has been performed within 8 weeks prior to Cycle 1, Day 1 and laboratory results are available. For those patients who have achieved a CR or cytopenic CR (including a CT scan indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR at least 8 weeks following the initial clinical assessment of CR. A bone marrow aspirate should be obtained for MRD assessment to confirm a molecular CR. Bone marrow examination should be performed as needed within 2 weeks for patients who show clinical suspicion for PD (ie, increased or de novo enlargement of liver, spleen, or lymph nodes on physical exam) in the absence of laboratory or histopathologic criteria for PD. Any additional/unscheduled bone marrow examinations performed during the study will be at the discretion of the investigator.

f Required for all women of reproductive potential (see inclusion criteria).

g HBsAg, IgG anti-HBcAb, and Hep C Ab serology (also HCV, and RNA by polymerase chain reaction if the patient is HCV antibody positive) required.

h Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count), platelet count, absolute neutrophil count, absolute lymphocyte count, and percent or absolute differential counts (eg, segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells). At baseline and all subsequent evaluations, cytopenias are to be graded per the National Cancer Institute Working Group Guidelines (see Appendix 18). All scheduled blood draws may be drawn up to 72 hours prior to the next planned evaluation.

i Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), a kaline phosphatase, lactate dehydrogenase, and uric acid. All scheduled blood draws may be drawn up to 72 hours prior to the next planned evaluation.

Appendix 1
Schedule of Assessments (cont.)

j Peripheral blood lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16, and CD56) measured by flow cytometry are required at baseline, interim assessment (within 14 days of Cycle 4, Day 1), early termination or end of treatment, 12 weeks after Day 1 of the last cycle of multi-agent therapy, and every 12 weeks thereafter.

k Consists of specific gravity, pH, blood, protein, glucose, ketones, and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

l Patients will have the following samples drawn at screening: serum for β2-microglobulin, whole blood for IgV_H mutational status, *p53* and other prognostic mutations, and interphase FISH for chromosomal abnormalities including 17p-, 11q-, 13q-, and trisomy +12. Sample will be taken for both local and central testing of 17p deletion by FISH.

m MRD samples collected at baseline, within 14 days of C4D1 (interim assessment) , end of treatment/early termination visit, and 3, 6 and 12 months after completion of combination therapy will be measured at a central laboratory.

n Whole blood predictive biomarker sample is required for all patients at screening and at time of progression (early termination if applicable) or at end of treatment, one tube each for protein and RNA analysis of Bcl-2 family members. A predictive bone marrow aspirate sample (1 mL each for protein and RNA analysis) should be drawn for all patients who have a bone marrow aspirate drawn at screening. For those patients for whom have a bone marrow examination has been performed within 8 weeks prior to Cycle 1, Day 1 and therefore do not need a bone marrow aspirate draw at screening, are not required to provide a predictive bone marrow aspirate sample.. Aspirate samples should be split from samples obtained for International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute Working Group or International Working Group criteria assessment whenever poss ble. If aspirate sample is limiting then protein should be prioritized over RNA sample. Please note that a bone marrow biopsy and aspirate is not required at the time of progression (unless it is needed to confirm or rule out PD); however, if it is performed then a predictive bone marrow biomarker sample should also be drawn. Predictive biomarker sample will be used for assessment of Bcl-2 family and other relevant markers by RNA and flow in the blood and bone marrow; and for Bcl-2:Bim complex by protein in blood.

o If formalin fixed specimen of bone marrow biopsy is collected at screening by the site as per standard clinical assessment of the patient, a sample should be provided for IHC analysis of Bcl-2 family.

p Residual tumor specimens are requested at screening and optional blood samples are requested at screening and at the end of multi-agent therapy visit or end of treatment/early termination visit for collection and storage at the Roche Clinical Repository.

q Rituximab will be administered at 375 mg/m^2 IV on Day 1 of Cycle 1 followed by 500 mg/m^2 IV on Day 1 of Cycles 2 through 6. Investigators will have the option of administering the rituximab dose for Day 1 of Cycle 1 over 2 days (eg, 100 mg IV on Day 1 of Cycle 1 followed by the remainder of the 375 mg/m^2 dose on Day 2 of Cycle 1).

r Bendamustine will be administered at 70 mg/m^2 IV on Days 1 and 2 of Cycles 1-6.

s The MDASI questionnaire will be completed at home on the specified days. The patients will be contacted by phone and an interactive voice response solution (IVRx) will be used to capture MDASI questionnaire data.

t Patients should complete the questionnaires prior to study drug administration and any other study assessments. PRO assessments should be performed prior to progression, at the time of progression, and at the first assessment after progression.

u An ECG is required at screening only and as clinically indicated for subsequent visits.

Appendix 2
Schedule of Pharmacokinetic Assessments

Patients Randomized to Arm A (GDC-0199+R)

Blood samples to assess GDC-0199 concentrations will be collected at the following time points:

Visit	Time point	Sample Type
Cycle 1, Day 1	Pre GDC-0199 dose 4 h (±1 h) post GDC-0199 dose	Plasma
Cycle 4, Day 1	Pre GDC-0199 dose 4 h (±1 h) post GDC-0199 dose	Plasma

Note: An unscheduled PK sample will be collected if TLS is observed.
An unscheduled PK sample will be collected in case of early termination.

Appendix 3
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

EORTC QLQ-C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Patient's identification number: _____
Patient's date of birth (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself, or using the toilet?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4

Appendix 3
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

Appendix 3
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Appendix 4
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-CLL16)

EORTC QLQ-CLL16
QOL.QLFORM='EORTC QLQ-CLL16'

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you lost weight?	1	2	3	4
32. Have you had a dry mouth?	1	2	3	4
33. Did you bruise?	1	2	3	4
34. Did you have abdominal discomfort?	1	2	3	4
35. Has your temperature been going up and down?	1	2	3	4
36. Did you have night sweats?	1	2	3	4
37. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
38. Did you feel ill or unwell?	1	2	3	4
39. Did you feel lethargic?	1	2	3	4
40. Have you felt “slowed down”?	1	2	3	4
41. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
43. Have you had trouble with chest infections?	1	2	3	4
44. Have you had trouble with other infections?	1	2	3	4
45. Have you needed repeated courses of antibiotics?	1	2	3	4
46. Have you worried about picking up an infection?	1	2	3	4

Appendix 5
M. D. Anderson Symptom Inventory (MDASI) Questionnaire

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

M. D. Anderson Symptom Inventory (MDASI – CLL - AMGEN)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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Page 1 of 2

MDASI-Core - English

Appendix 5
M. D. Anderson Symptom Inventory (MDASI) Questionnaire (cont.)

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
14. Your night sweats at their WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Fevers and chills at their WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Lymph node swelling at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your diarrhea at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your bruising easily or bleeding at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your constipation at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	DID NOT INTERFERE 0	1	2	3	4	5	6	7	8	9	INTERFERED COMPLETELY 10
20. General activity?	○	○	○	○	○	○	○	○	○	○	○
21. Mood?	○	○	○	○	○	○	○	○	○	○	○
22. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
23. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
24. Walking?	○	○	○	○	○	○	○	○	○	○	○
25. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

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MDASI-Core - English

DRAFT

Appendix 6
EQ-5D (U.S. Version)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

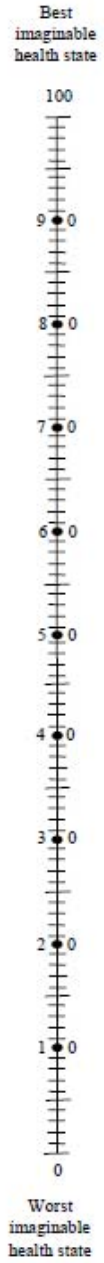
2

Appendix 6
EQ-5D (U.S. Version) (cont.)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

Appendix 7
ECOG Performance Status Scale

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

Appendix 8
Treatment Options for CLL (Adapted from NCCN Version 3.2012 and 2011 ESMO Clinical Practice Guidelines)

CLL Treatment Options per NCCN Guidelines (v 3.2012)

Treatment Options for Patients WITHOUT the 17p deletion		
Front-line		
Frail patients with significant comorbidities	Age ≥ 70 or younger with significant comorbidities	Age < 70 or older patients without significant comorbidities

• Chlorambucil ± rituximab
• Single agent rituximab
• Pulsed corticosteroids
	• Chlorambucil ± rituximab
	• Bendamustine + rituximab
	• Cyclophosphamide, prednisone ± rituximab
	• Alemtuzumab
	• Single agent rituximab
	• Fludarabine ± rituximab
	• Cladribine
		• Chemoimmunotherapy
		  ○ FCR
		  ○ FR
		  ○ PCR
		  ○ BR

Relapsed/Refractory Disease		
Long duration of response (18-36 months)	Short response and age ≥ 70	Short response for age < 70 or older patients without significant comorbidities
• Retreat with first line therapy	• Reduced dose FCR or PCR • BR • HDMP + rituximab • Chlorambucil ± rituximab • Ofatumumab • Alemtuzumab ± rituximab • Dose dense rituximab (cat 2B)	• Chemoimmunotherapy (eg, FCR, PCR, BR, fludarabine + alemtuzumab, CHOP, HyperCVAD, OFAR, dose adjusted EPOCH) • Ofatumumab • Alemtuzumab ± rituximab • HDMP + rituximab

Appendix 8
Treatment Options for CLL (Adapted from NCCN Version 3.2012 and 2011 ESMO Clinical Practice Guidelines) (cont.)

CLL Treatment Options per NCCN Guidelines (v 3.2012) (cont.)

Treatment Options for Patients WITH the 17p deletion
Front-line
• FCR • FR • HDMP + rituximab • Alemtuzumab ± rituximab
Relapsed/Refractory Disease
• Alemtuzumab ± rituximab • CHOP • CFAR • HDMP ± rituximab • HyperCVAD • Ofatumumab • OFAR

Appendix 8
Treatment Options for CLL (Adapted from NCCN Version 3.2012 and 2011 ESMO Clinical Practice Guidelines) (cont.)

CLL Treatment Options per ESMO Guidelines (adapted from Eichhorst et al. 2011)

Treatment Options for Patients WITHOUT the 17p deletion		
Front-line		
Good PS	Poor PS	
• FCR	• Chlorambucil	
Relapsed/Refractory Disease		
Early Relapse (< 12-24 months to relapse after monotherapy or < 24-36 months to relapse after chemoimmunotherapy)		
Good PS after chemoimmunotherapy	Good PS after monotherapy	Poor PS
• Alemtuzumab ± fludarabine or BR followed by ASCT	• FCR	• FCR • bendamustine • alemtuzumab • ofatumumab • HDMP + rituximab
Late Relapse (> 12-24 months after monotherapy or > 24-36 months after chemoimmunotherapy)		
Any PS: repeat first–line therapy		

Treatment Options for Patients WITH the 17p deletion	
Frontline	
Good PS	Poor PS
• FCR or aletuzumab ± fludarabine followed by ASCT	• Alemtuzumab
Relapsed/Refractory Disease	
Good PS	Poor PS
• Alemtuzumab ± fludarabine followed by ASCT	• Alemtuzumab

ASCT: allogeneic stem cell transplantation; BR: bendamustine, rituximab; CFAR: cyclophosphamide, fludarabine, alemtuzumab, rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CLL: chronic lymphocytic leukemia; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ESMO: European Society for Medical Oncology; FCR: fludarabine, cyclophosphamide, rituximab; FR: fludarabine, cyclophosphamide; HDMP: high-dose methylprednisolone; HyperCVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, cytarabine; NCCN: National Comprehensive Cancer Network; OFAR: oxaliplatin, fludarabine, cytarabine, rituximab; PCR: pentostatin, cyclophosphamide, rituximab; PS: performance status.

Appendix 9
Sample List of Excluded and Cautionary Medications

Excluded	**CYP3A Inducers–Weak/Moderate (Cautionary)**
warfarin (Coumadin)[a]	barbiturates
other investigational agents[b]	efavirenz
steroid therapy for anti-neoplastic intent	nevirapine
	oxcarbazepine
CYP3A Inhibitors (Excluded)	rifapentine,
atanazavir	troglitazone
clarithromycin	
indinavir	**CYP2C8 Substrates[c] (Cautionary)**
itraconazole	amiodarone
fluvoxamine (Luvox)	amodiaquine
ketoconazole	cerivastatin
nefazodone	chloroquine
nelfinavir	lovastatin[d]
ritonavir	pioglitazone
saquinavir	repaglinide
telithromycin	rosiglitazone
voriconazole	simvastatin (Zocor)[d]
fluconazole (Diflucan)	
	CYP2C9 Substrates (Cautionary)
CYP3A Inducers – Potent (Excluded)	celecoxib
avasimibe	diclofenac
carbamazepine (Tegretol®)	fluvastatin
mitotane	glipizide
phenobarbital	irbesarten
phenytoin (Dilantin®)	losartan
rifabutin	phenytoin
rifampin (Rifadin®)	sulfamethoxazole
St. John's Wort	sulfinpyrazone
	tolbutamide
	torsemide

[a] Warfarin is also a CYP2C9 substrate.
[b] Including targeted small-molecule agents.
[c] Only certain statins qualify as CYP2C8 substrates.
[d] Significant increase in AUC by co-administration of gemfibrozile, a potent CYP2C8 inhibitor. However, the involvement of CYP2C8 is unclear.

Appendix 9
Sample List of Excluded and Cautionary Medications (cont.)

Commonly Used CYP1A2 Inhibitors and Inducers (Drugs, Foods, Over-the-Counter Medications and Supplements)

Based on the USPI for bendamustine, no formal clinical assessments of pharmacokinetic drug – drug interactions between bendamustine and other drugs have been conducted. Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (eg, fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (eg, omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites.

The medications listed below are not contraindicated; however, caution should be used or alternative treatments with medications that are not CYP1A2 inhibitors or inducers should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed for your patient's medical condition. This list is not exhaustive.

CYP1A2 Inhibitors (cautionary)	CYP1A2 Inducers (cautionary)
Amiodarone	Cruciferous vegetables (broccoli, cauliflower, arugula, brussel sprouts, cabbage, kale, chard, turnips, radishes, wasabi, bok choy, watercress, collard greens)
Cimetidine	Char-grilled meat
Ciprofloxacin	Beta-naphthoflavone
Fluoroquinolones	Methylcholanthrene
Fluvoxamine	Modafinil
Furafylline	Nafcillin
Interferon	Omeprazole
Methoxsalen	Smoking/tobacco
Mibefradil	

The bendamustine USPI recommends that caution be used or alternative treatments be considered if treatment with one of these listed drugs or substances or another CYP1A2 inhibitor or inducer is needed. Please contact the study principal investigator if you have further questions.

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Appendix 10
Cairo – Bishop Definition and Grading of Tumor Lysis Syndrome

From Cairo and Bishop 2004.

Cairo – Bishop Definition of Laboratory Tumor Lysis Syndrome

Uric Acid	≥ 476 μmol/L (≥ 8.0 mg/dL) or 25% increase from baseline
Potassium	≥ 6.0 mmol/L (≥ 6.0 mEq/L) or 25% increase from baseline
Phosphorous	≥ 1.45 mmol/L (≥ 4.5 mg/dL) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/L (≤ 7.0 mg/dL) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

Cairo – Bishop Definition of Clinical Tumor Lysis Syndrome

The presence of laboratory TLS and one or more of the following criteria:
Creatinine: ≥ 1.5 ULN (age > 12 years or age-adjusted)
Cardiac arrhythmia / sudden death
Seizure[a]

ULN: upper limit of normal.

[a] Not directly attributable to a therapeutic agent.

Appendix 11
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia

Based on iwCLL guidelines (Hallek et al. 2008)

Complete Response

Complete response (CR) requires all of the following criteria as assessed no earlier than 2 months after completion of therapy:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4000/μL)
- Absence of lymphadenopathy (nodes $\leq$ 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)
- Blood counts above the following values
  - Neutrophils $> 1.5 \times 10^9$/L (1500/μL) (without growth factors)
  - Platelets $> 100 \times 10^9$/L (100 000/μL) (without platelet transfusion or growth factors)
  - Hemoglobin $>$ 110 g/L (11 g/dL) (without blood transfusions or erythropoietin)
- Bone marrow at least normocellular for age, with $<$ 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. Bone-marrow aspirate and biopsy should be performed 3 months after last treatment when clinical and laboratory results listed above demonstrate that a CR/cytopenic CR has been achieved. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. A marrow biopsy should be compared with a pretreatment marrow if available. Patients who are otherwise in a CR but whose bone marrow nodules can be identified histologically should be considered to be in partial response (PR [nodal PR]). Immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than or chronic lymphocytic leukemia (CLL) cells.

Complete Response with Incomplete Bone Marrow Recovery

For patients who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenia, the marrow evaluation described above should be performed with scrutiny and should not show any clonal infiltrate.

Appendix 11
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

Partial Response

To be considered PR, patients must exhibit the following features for at least 2 months. At least two of the following criteria must be met:

- ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment value.
- ≥ 50% reduction in lymphadenopathy (sum of longest diameter of the 6 largest lymph nodes by physical examination and 50% reduction in the sum of product of diameter of 6 largest lymph nodes measured by computed tomography [CT] scan). There should be no increase in any node and no new enlarged lymph node. In small lymph nodes (< 2 cm in diameter), an increase of less than 25% is not considered to be significant.
- ≥ 50% reduction of liver and/or spleen enlargement if enlarged at baseline as assessed by physical examination.

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

- Neutrophils > 1.5×10^9/L (1500/μL) (without growth factors) or ≥ 50% of pretreatment value
- Platelets > 100×10^9/L (100 000/μL) (without platelet transfusion or growth factors) or ≥ 50% of pretreatment value
- Hemoglobin > 110 g/L (11 g/dL) (without blood transfusions or erythropoietin) or ≥ 50% of pretreatment value

Progressive Disease

Progressive disease (PD) during or after therapy will be characterized by at least one of the following:

- ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5×10^9/L.
  - During treatment, the increase should be assessed against Cycle 1, Day 1 (precycle) lymphocyte count and not - cycle lymphocyte counts, which may not be stable.
  - After treatment, the increase should be assessed against the lymphocyte count assessed at the first follow-up visit, after the end of treatment.
- Appearance of new palpable lymph nodes (> 15 mm in longest diameter) or any new extra-nodal lesion (regardless of size)
- ≥ 50% increase in the longest diameter of any previous site of lymphadenopathy

Appendix 11
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

- $\geq$ 50% increase in the enlargement of the liver and/or spleen as determined by measurement below the relevant costal margin or appearance of palpable hepatomegaly or splenomegaly that was not previously present
- Transformation to a more aggressive histology (eg, Richter syndrome or plasmacytoid lymphocytic lymphoma with $>$ 55% prolymphocytes); whenever possible, this diagnosis to be supported by lymph node biopsy

After treatment, the progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL) or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100 000/μL), that occurs no earlier than 3 months after end of therapy defines progression if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease

Patients who have not achieved a CR or a PR or who have not exhibited PD will be considered to have stable disease.

Appendix 12
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

1. FIRST DOSE OF GDC-0199 OR DOSE INCREASE

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional GDC-0199 doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not < 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be as per institutional protocols.

In addition to the recommendations in the table below, for patients with CLL/SLL receiving first dose of GDC-0199:

- For potassium increase $\geq$0.5 mmol/L from baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of $>$0.5 mg/dL AND $>$4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

Appendix 12
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still <upper limit of normal (ULN), manage as per potassium ≥ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium <ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium >upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV×1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If potassium <ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV×1. • Administer insulin 0.1 U/kg IV+D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq IV push. ○ If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.

Appendix 12
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus ⩾ 10 mg/dL) • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Appendix 12
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Abnormality	Management Recommendations
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours STAT.

2. ONGOING DOSING OF GDC-0199

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (eg, 48 or 72 hours) are as below. Note: If the patient is hospitalized, no additional GDC-0199 doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
  - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further GDC-0199 dosing.
- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

PROTOCOL

TITLE:	**A MULTICENTER, PHASE III, OPEN-LABEL, RANDOMIZED STUDY IN RELAPSED/REFRACTORY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TO EVALUATE THE BENEFIT OF GDC-0199 (ABT-199) PLUS RITUXIMAB COMPARED WITH BENDAMUSTINE PLUS RITUXIMAB**
PROTOCOL NUMBER: GO28667	**VERSION NUMBER:** 7
EUDRACT NUMBER: 2013-002110-12	**IND NUMBER:** 110159
TEST PRODUCT:	Venetoclax (GDC-0199 [ABT-199]; (RO5537382)
MEDICAL MONITOR:	[redacted]
SPONSORS:	F. Hoffmann-La Roche Ltd and AbbVie Inc. will act as co-sponsors of this trial globally.*
DATE FINAL:	Version 1: 7 August 2013
DATES AMENDED:	Version 2: 26 November 2013 Version 3 (Korea): 28 February 2014 Version 4: 10 June 2014 Version 5: 16 October 2014 Version 6: 20 June 2016 *Version 7: See electronic date stamp below*

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	21-Nov-2016 21:25:01

CONFIDENTIAL

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PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- *The description of the fixed sequence testing of the secondary efficacy endpoints in the statistical section of the protocol was streamlined and the details of the testing of secondary endpoints will be set out in the statistical analysis plan, in accordance with the international guideline on Statistical Principles for Clinical Trials (ICH E9). This amendment is implemented to allow for a change in the clinical prioritization of the secondary efficacy endpoints to mirror the evolving R/R CLL therapeutic and scientific landscape.*
- *Minor changes have been made to improve clarity and consistency of the secondary efficacy endpoints.*
- *The sample list of prohibited and cautionary medications in Appendix 9 has been updated, incorporating the FDA's updated guidelines*

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This version of the protocol represents cumulative changes from all previous amendments to the protocol.

PROTOCOL AMENDMENT, VERSION 7: SUMMARY OF CHANGES

GLOBAL CHANGES

The Medical Monitor was updated from [redacted] to [redacted]

Section 6.4.2 Secondary Efficacy Endpoints

If the study meets its primary endpoint of prolonging PFS assessed by the investigator in all randomized patients, then formal statistical tests of *few key secondary efficacy endpoints will be performed. Other secondary endpoints will not be tested formally. Further details of the fixed sequence testing will be described in the Statistical Analysis Plan.*

Secondary efficacy outcome measures include:

- *Investigator-assessed PFS in patients with 17p deletion per central laboratory FISH test*
- *IRC-assessed PFS in patients with 17p deletion per central laboratory detection*
- *Investigator-assessed best OR rate, CR, CRi, nPR, and PR rates*
- *IRC-assessed best OR rate, CR, CRi, nPR, and PR rates*
- *OS, defined as the time from the date of randomization to the date of death from any cause. Patients who were not reported as having died at the time of the analysis will be censored at the date when they were last known to be alive as documented by the investigator.*
- EFS, defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-CLL treatment. *If the specified event (disease progression/relapse, death, start of a new anti-CLL treatment) does not occur, patients will be censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS will be censored at the time of randomization.*
- DOR, defined for patients with a best OR of CR, CRi, nPR, or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse as assessed by the investigator or death from any cause. *For patients achieving a response who have not progressed, relapsed, or died at the time of analysis, DOR will be censored on the date of last response assessment. Patients who have never had responded will not be included in this analysis.*
- TTNT, defined as the time from randomization to start of new non-protocol anti–*CLL* therapy or death from any cause. *For patients who have not received the next anti-CLL treatment or died at the time of analysis, TTNT will be censored at the date when the patient was last known to be alive without having received additional anti-lymphoma treatment.*

Appendix 9: Sample list of prohibited and cautionary medications

Appendix 9 has been revised to update the list of prohibited and cautionary medications as per FDA's updated guidelines.

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM 12

PROTOCOL SYNOPSIS 13

1. BACKGROUND 34
   - 1.1 Background on Chronic Lymphocytic Leukemia 34
   - 1.2 Background on Venetoclax (GDC-0199) 34
   - 1.2.1 Bcl-2 Protein Family 34
   - 1.2.2 Venetoclax 35
   - 1.2.2.1 Venetoclax Nonclinical Activity and Pharmacokinetic Profile 35
   - 1.2.2.2 Venetoclax Nonclinical Toxicology 36
   - 1.2.2.3 Venetoclax Clinical Experience 38
   - 1.2.2.4 Clinical Pharmacokinetics and Pharmacodynamics 46
   - 1.3 Study Rationale and Benefit-Risk Assessment 48

2. OBJECTIVES 50
   - 2.1 Efficacy Objectives 50
   - 2.2 Safety Objective 51
   - 2.3 Pharmacodynamic Objective 51
   - 2.4 Pharmacokinetic Objective 51
   - 2.5 Patient-Reported Outcome Objectives 51
   - 2.6 Health Economic Objective 51
   - 2.7 Exploratory Objectives 51

3. STUDY DESIGN 52
   - 3.1 Description of Study 52
   - 3.1.1 Independent Review Committee 55
   - 3.1.2 Independent Data Monitoring Committee 55
   - 3.2 End of Study 55
   - 3.3 Rationale for Study Design 55
   - 3.3.1 Rationale for Combination Therapy (Experimental Group) 55
   - 3.3.1.1 Rationale for Venetoclax Dosage 56

3.3.1.2 Rationale for Rituximab Dosage 56
3.3.1.3 Rationale for Duration of Therapy 56
3.3.2 Rationale for Control Group 57
3.3.2.1 Rationale for BR Dosage 57
3.3.3 Rationale for Patient Population 58
3.3.4 Rationale for Including Patients with 17p Deletion 59
3.3.5 Rationale for Biomarker Assessments 60
3.3.6 Rationale for Patient-Reported Outcome Assessments 60
3.4 Outcome Measures 61
3.4.1 Efficacy Outcome Measures 61
3.4.1.1 Primary Efficacy Outcome Measure 61
3.4.1.2 Secondary Efficacy Outcome Measures 61
3.4.2 Safety Outcome Measures 61
3.4.3 Pharmacodynamic Outcome Measure 62
3.4.4 Pharmacokinetic Outcome Measures 62
3.4.5 Patient-Reported Outcome Measures 62
3.4.6 Health Economic Outcome Measure 62
3.4.7 Exploratory Outcome Measures 62

4. MATERIALS AND METHODS 62
4.1 Patients 62
4.1.1 Inclusion Criteria 63
4.1.2 Exclusion Criteria 65
4.2 Method of Treatment Assignment and Blinding 67
4.3 Study Treatment 67
4.3.1 Formulation, Packaging, and Handling 67
4.3.1.1 Venetoclax 67
4.3.1.2 Rituximab 68
4.3.1.3 Bendamustine 68
4.3.2 Dosage, Administration, and Compliance 69
4.3.2.1 Venetoclax 69
4.3.2.2 Rituximab 70
4.3.2.3 Bendamustine 72

4.3.3 Investigational Medicinal Product Accountability 73
4.3.4 Post-Trial Access to Venetoclax 73
4.4 Concomitant Therapy and Food 74
4.4.1 Permitted Therapy 74
4.4.1.1 Premedication before Rituximab 74
4.4.1.2 Prophylaxis and Management of Tumor Lysis Syndrome 75
4.4.1.3 Prophylaxis for Infections 85
4.4.1.4 Prophylaxis of Hepatitis B Reactivation 85
4.4.2 Prohibited and Cautionary Therapy 85
4.4.3 Prohibited Food 86
4.5 Study Assessments 86
4.5.1 Description of Study Assessments 86
4.5.1.1 Medical History and Demographic Data 86
4.5.1.2 Physical Examinations 87
4.5.1.3 Vital Signs and ECOG Performance Status 87
4.5.1.4 Electrocardiogram 87
4.5.1.5 Assessment of Left Ventricular Ejection Fraction 88
4.5.1.6 Tumor and Response Evaluations 88
4.5.1.7 Laboratory Assessments 89
4.5.1.8 Patient-Reported Outcomes 91
4.5.1.9 Samples for Roche Clinical Repository 93
4.5.2 Timing of Study Assessments 95
4.5.2.1 Screening and Pretreatment Assessments 95
4.5.2.2 Assessments during Treatment 96
4.5.2.3 Assessments at Early Treatment Termination Visit 96
4.5.2.4 Follow-Up Assessments 96
4.5.2.5 Assessments at Unplanned Visits 96
4.6 Patient, Study, and Site Discontinuation 97
4.6.1 Patient Discontinuation 97
4.6.1.1 Discontinuation from Study Drug/Treatment 97
4.6.1.2 Withdrawal from Study 98
4.6.2 Study and Site Discontinuation 98

5. ASSESSMENT OF SAFETY 98
5.1 Safety Plan 98
5.1.1 Risks Associated with Venetoclax 98
5.1.1.1 Tumor Lysis Syndrome 99
5.1.1.2 Cytopenia 99
5.1.1.3 Infectious Complications 99
5.1.1.4 Effects on Cardiac Function 99
5.1.1.5 Effects on Fertility 100
5.1.1.6 Drug Interactions 100
5.1.2 Risks Associated with Rituximab Therapy 100
5.1.2.1 Infusion-Related Reactions 100
5.1.2.2 Tumor Lysis Syndrome 100
5.1.2.3 Hepatitis B Reactivation 100
5.1.2.4 Progressive Multifocal Leukoencephalopathy 102
5.1.2.5 Cardiac Toxicity 102
5.1.2.6 Infection 102
5.1.2.7 Severe Mucocutaneous Reactions 102
5.1.2.8 Bowel Obstruction and Perforation 102
5.1.3 Risks Associated with Bendamustine 103
5.1.3.1 Myelosuppression 103
5.1.3.2 Infection 103
5.1.3.3 Infusion Reactions 103
5.1.3.4 Tumor Lysis Syndrome 103
5.1.3.5 Cutaneous Reactions 103
5.1.3.6 Long-Term Stem-Cell Toxicity 103
5.1.3.7 Extravasation of Bendamustine 104
5.1.3.8 Transfusion-Associated Graft versus Host Disease 104
5.1.3.9 Drug Interactions 104
5.1.4 Risks Associated with Venetoclax and Rituximab Combination Therapy 104
5.1.5 Management of Specific Adverse Events 104
5.2 Safety Parameters and Definitions 110
5.2.1 Adverse Events 111

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) ... 111
5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor) ... 112
5.3 Methods and Timing for Capturing and Assessing Safety Parameters ... 112
5.3.1 Adverse Event Reporting Period ... 112
5.3.2 Eliciting Adverse Event Information ... 113
5.3.3 Assessment of Severity of Adverse Events ... 113
5.3.4 Assessment of Causality of Adverse Events ... 114
5.3.5 Procedures for Recording Adverse Events ... 114
5.3.5.1 Diagnosis versus Signs and Symptoms ... 114
5.3.5.2 Adverse Events Occurring Secondary to Other Events ... 115
5.3.5.3 Persistent or Recurrent Adverse Events ... 115
5.3.5.4 Abnormal Laboratory Values ... 115
5.3.5.5 Abnormal Vital Sign Values ... 116
5.3.5.6 Abnormal Liver Function Tests ... 117
5.3.5.7 Deaths ... 117
5.3.5.8 Preexisting Medical Conditions ... 118
5.3.5.9 Lack of Efficacy or Worsening of CLL ... 118
5.3.5.10 Hospitalization or Prolonged Hospitalization ... 118
5.3.5.11 Overdoses ... 119
5.3.5.12 Patient-Reported Outcome Data ... 119
5.4 Immediate Reporting Requirements from Investigator to Sponsor ... 119
5.4.1 Emergency Medical Contacts ... 120
5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest ... 121
5.4.3 Reporting Requirements for Pregnancies ... 121
5.4.3.1 Pregnancies in Female Patients ... 121
5.4.3.2 Pregnancies in Female Partners of Male Patients ... 121
5.4.3.3 Abortions ... 122
5.4.3.4 Congenital Anomalies/Birth Defects ... 122

5.5 Follow-Up of Patients after Adverse Events 122
5.5.1 Investigator Follow-Up 122
5.5.2 Sponsor Follow-Up 123
5.6 Post-Study Adverse Events 123
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 123

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 124
6.1 Determination of Sample Size 124
6.2 Summaries of Conduct of Study 125
6.3 Summaries of Treatment Group Comparability 125
6.4 Efficacy Analyses 125
6.4.1 Primary Efficacy Endpoint 125
6.4.2 Secondary Efficacy Endpoints 126
6.5 Safety Analyses 127
6.6 Pharmacodynamic Analyses 128
6.7 Pharmacokinetic Analyses 128
6.8 Patient-Reported Outcome Analyses 129
6.9 Health Economic Analysis 129
6.10 Exploratory Analyses 129
6.11 Interim Analyses 130

7. DATA COLLECTION AND MANAGEMENT 130
7.1 Data Quality Assurance 130
7.2 Electronic Case Report Forms 131
7.3 Electronic Patient-Reported Outcome Data 131
7.4 Source Data Documentation 132
7.5 Use of Computerized Systems 132
7.6 Retention of Records 133

8. ETHICAL CONSIDERATIONS 133
8.1 Compliance with Laws and Regulations 133
8.2 Informed Consent 133
8.3 Institutional Review Board or Ethics Committee 134
8.4 Confidentiality 135

8.5 Financial Disclosure 135

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 135

9.1 Study Documentation 135

9.2 Protocol Deviations..... 136

9.3 Site Inspections 136

9.4 Administrative Structure..... 136

9.5 Publication of Data and Protection of Trade Secrets 136

9.6 Protocol Amendments 137

10. REFERENCES 138

LIST OF TABLES

Table 1 Administration of First and Subsequent Infusions of Rituximab 72
Table 2 Summary of TLS Prophylaxis and Monitoring Measures 82
Table 3 Dose Modifications for Hematologic Toxicity during the Combination Therapy Period (Venetoclax + Rituximab) and/or Venetoclax Monotherapy 105
Table 4 Dose Modifications for Non-Hematologic Toxicity during the Combination Therapy Period (Venetoclax + Rituximab) and/or Venetoclax Monotherapy 107
Table 5 Venetoclax Dose Reduction..... 108
Table 6 Bendamustine Dose Reduction..... 109
Table 7 Dose Modification Guidelines for Bendamustine..... 110
Table 8 Adverse Event Severity Grading Scale 113

LIST OF FIGURES

Figure 1 Study M12-175: Preliminary Mean (+ SD) Venetoclax Plasma Concentration–Time Profiles Following Oral Administration of Venetoclax (GDC-0199 [ABT-199]) in Patients with CLL/SLL (Log-Linear Scale) 47
Figure 2 Study Schema..... 53
Figure 3 Venetoclax Dosing Scheme during the Ramp-Up Period 69

LIST OF APPENDICES

Appendix 1 Schedule of Assessments 143
Appendix 2 Schedule of Pharmacokinetic Assessments 177
Appendix 3 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) 178
Appendix 4 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-CLL16) 181
Appendix 5 M.D. Anderson Symptom Inventory (MDASI) Questionnaire 182
Appendix 6 EQ-5D (U.S. Version) 184
Appendix 7 ECOG Performance Status Scale 186
Appendix 8 Treatment Options for CLL (Adapted from NCCN Version 4.2014 and 2011 ESMO Clinical Practice Guidelines) 187
Appendix 9 Sample List of Prohibited and Cautionary Medications 190
Appendix 10 Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia 193
Appendix 11 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome 201
Appendix 12 National Cancer Institute–Sponsored Working Group Hematologic Adverse Event Grading Scale for Chronic Lymphocytic Leukemia for Patients with Baseline Abnormal Hematologic Laboratories 205
Appendix 13 Adverse Events Commonly Associated with CLL Study Population and/or Progression of CLL 206

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, PHASE III, OPEN-LABEL, RANDOMIZED STUDY IN RELAPSED/REFRACTORY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TO EVALUATE THE BENEFIT OF GDC-0199 (ABT-199) PLUS RITUXIMAB COMPARED WITH BENDAMUSTINE PLUS RITUXIMAB**
PROTOCOL NUMBER:	GO28667
VERSION NUMBER:	*7*
EUDRACT NUMBER:	2013-002110-12
IND NUMBER:	110159
TEST PRODUCT:	Venetoclax (GDC-0199 *[*ABT-199*];* RO5537382)
MEDICAL MONITOR:	[redacted]
SPONSORS:	F. Hoffmann-La Roche Ltd and AbbVie Inc. will act as co-sponsors of this trial globally.*

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, PHASE III, OPEN-LABEL, RANDOMIZED STUDY IN RELAPSED/REFRACTORY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TO EVALUATE THE BENEFIT OF GDC-0199 (ABT-199) PLUS RITUXIMAB COMPARED WITH BENDAMUSTINE PLUS RITUXIMAB**
PROTOCOL NUMBER:	GO28667
VERSION NUMBER:	7
EUDRACT NUMBER:	2013-002110-12
IND NUMBER:	110159
TEST PRODUCT:	Venetoclax (GDC-0199 [ABT-199}; RO5537382)
PHASE:	III
INDICATION:	Chronic Lymphocytic Leukemia
SPONSORS:	F. Hoffmann-La Roche Ltd and AbbVie Inc. will act as co-sponsors of this trial globally.*

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of venetoclax and rituximab (venetoclax +R) compared with bendamustine and rituximab (BR) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) as measured by investigator-assessed progression-free survival (PFS).

The secondary efficacy objectives for this study are as follows:

- To analyze Independent Review Committee (IRC)-assessed PFS in the subset of CLL patients with 17p deletion identified by fluorescence in situ hybridization (FISH) testing performed at a central laboratory
- To evaluate PFS as assessed by an IRC
- To analyze investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing performed at a central laboratory
- To evaluate rate of best overall response (OR; defined as complete response [CR], complete response with incomplete marrow recovery [CRi], nodular partial response [nPR], and partial response [PR]), as assessed by the investigator
- To evaluate rates of OR rate, CR, CRi, nPR, and PR at end of combination treatment response visit, as assessed by the investigator
- To evaluate OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit, as assessed by the IRC

- To evaluate overall survival (OS)
- To evaluate event-free survival (EFS)
- To evaluate duration of response (DOR) for patients with a best overall response of CR, CRi, nPR, or PR
- To evaluate time to next anti-CLL treatment (TTNT)
- To evaluate the proportion of patients with minimal residual disease (MRD) negativity at the disease response assessment timepoints

Safety Objective

The safety objective for this study is as follows:

- To evaluate the safety of venetoclax and rituximab compared with BR in patients with relapsed or refractory CLL, focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities

Pharmacodynamic Objective

The pharmacodynamic objective for this study is as follows:

- To assess changes in lymphocyte subset counts during the study (e.g., T and B cells)

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of venetoclax in patients with relapsed or refractory CLL

Patient-Reported Outcome Objectives

The patient-reported outcome (PRO) objectives for this study are as follows:

- To compare treatment-related symptoms following treatment with venetoclax and rituximab compared with BR in patients with relapsed or refractory CLL, as measured by M. D. Anderson Symptom Inventory (MDASI) and European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and associated CLL module (QLQ-CLL16)
- To evaluate changes from baseline CLL symptoms scores using MDASI and EORTC QLQ-C30 and QLQ-CLL16 questionnaires
- To evaluate time to disease-related symptom progression using EORTC QLQ-CLL16 health-related quality of life (HRQoL) using global health status/quality of life (QOL) and other functional subscales of QLQ-C30
- To assess interference of treatment and disease-related symptoms on QOL using the MDASI questionnaire

Health Economic Objective

The health economic objective for this study is as follows:

- To compare the health economic effects of venetoclax in combination with rituximab versus BR in patients with relapsed or refractory CLL. The EuroQol 5 Dimension (EQ-5D) questionnaire will be used to support health economic/pharmacoeconomic analyses and will be analyzed post hoc.

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the relationship between efficacy outcome and potential biomarkers, including Bcl-2 expression, for patients treated with venetoclax and rituximab compared with BR
- To evaluate potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with venetoclax and rituximab or with BR

Study Design

Description of Study

This is an open-label, international, multicenter, randomized, phase III study to investigate the efficacy and safety of venetoclax in combination with rituximab (venetoclax+R) compared with bendamustine in combination with rituximab (BR) in patients with relapsed or refractory CLL.

Approximately 370 patients will be recruited from approximately 150 centers in up to 29 countries and randomly assigned in 1:1 ratio to receive either venetoclax+R (Arm A) or BR (Arm B). Randomization will be stratified according to the following factors:

- 17p deletion: yes or no
- Risk status: high risk or low risk

  High risk: defined as harboring 17p deletion or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy

  Low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemotherapy or chemoimmunotherapy.
- Geographic region: United States/Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America.

Patients randomized to Arm A (venetoclax + R) will have a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg daily. Following the venetoclax ramp-up period, patients will receive 6 cycles of rituximab consisting of a single infusion on the first day of each 28-day cycle. Patients will continue to take their daily dose of venetoclax during the rituximab cycles. Patients who have not progressed following the completion of the 6 cycles will continue to receive venetoclax until disease progression or for a maximum of 2 years from Cycle 1 Day 1.

Patients randomized to Arm B (BR) will receive 6 cycles of BR consisting of a single infusion of rituximab on Day 1 and bendamustine infusions on Days 1 and 2 of each 28-day cycle.

All patients will have baseline tumor assessment and will be assessed for response to treatment by the investigator using standard clinical and laboratory examinations and computed tomography (CT) scans according to international workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines at screening and at the following timepoints (selected to mirror those used in current phase III CLL protocols [CLL10, CLL11]):

- Clinical response assessment only on Day 1 of every cycle of combination therapy
- Full response assessment, including CT scans, at interim response assessment (within 14 days of Cycle 4 Day 1)
- Clinical response assessment only at completion of combination therapy (4 weeks ± 7 days after Day 1 of the last cycle of rituximab + venetoclax [Arm A] or BR [Arm B] or Day 1 of the last treatment cycle in case of early termination)
- Full response assessments, including CT scans, at 8–12 weeks after combination therapy (defined as 8–12 weeks after Day 1 of Cycle 6 or 8–12 weeks after Day 1 of the last cycle for early termination).

Following 6 cycles of combination therapy, patients in both arms will be followed clinically every 3 months through Year 3 from initiation of combination therapy (Cycle 1 Day 1). Patients will then be followed every 6 months for an additional 2 years, study withdrawal, or end of study, whichever comes first. At each follow-up visit, patients will be assessed for response/progression by clinical assessment only. In addition, at any time during the study when clinical or laboratory findings suggest that the response may have improved from stable disease (SD) to PR, or from PR to CR, imaging should be performed to confirm the response. Imaging is not routinely required to determine progressive disease (PD), as objective evidence of PD is most often documented by measurement of elevated peripheral CLL cells. However, when PD cannot be documented by increasing peripheral blood counts, imaging is required to

document PD detected by physical examination or suspected based on symptoms. A bone marrow biopsy may also be conducted at any time during the study to confirm a CR.

A bone marrow aspirate should be obtained for MRD assessment in all responders (CR+PR) at the End of Combination Treatment Response Visit. In addition, MRD samples in the peripheral blood are collected at baseline, within 14 days of C4D1 (interim assessment), completion of combination therapy/early treatment termination visit (if applicable), End of Combination Treatment Response Visit, and at the timepoints specified in Appendix 1 during the follow-up or at any visit during the follow-up where a patient has a response (PR or CR status). Samples will be measured at a central laboratory.

After 5 years in the study or after disease progression during the follow-up period (whichever comes first), patients will be followed annually for OS, PD (if not progressed already), and new anti-CLL therapy until the end of study. Annual follow-up may be conducted by telephone contact.

Patients who receive a new anti-CLL therapy any time during follow-up in the absence of PD will be followed on the same schedule of assessment (see protocol) for PD and then for OS.

Patients who discontinue all components of study therapy either prior to completion of planned therapy or prior to disease progression (e.g., for toxicity) will continue to be followed for MRD levels, PD, and OS (regardless of whether they subsequently receive new anti-CLL therapy).

An independent review of the responses of all patients will also be conducted to confirm the primary PFS endpoint, including blinded review of clinical and laboratory findings as well as blinded radiology review of imaging assessments.

Number of Patients

Approximately 370 patients will be recruited from approximately 150 centers in up to 29 countries and randomly assigned in 1:1 ratio to receive either venetoclax+R (Arm A) or BR (Arm B).

Target Population

The target population for this study is adult patients with relapsed or refractory CLL requiring treatment. Patients must meet the following criteria for study entry:

- Signed informed consent.
- Age ≥ 18 years.
- Diagnosis of CLL that meets published diagnostic criteria. Patients must have peripheral blood B-lymphocyte counts which clonally express CD5, CD19/20, and CD23 and are either kappa or lambda light-chain-restricted. Pro-lymphocytes may comprise no more than 55% of total circulating lymphocytes. At initial diagnosis of CLL (i.e., prior to front-line treatment), the peripheral lymphocyte count must have been > 5000/mm3. Patients must meet the following criteria for relapsed or refractory CLL (per the iwCLL guidelines:

    Relapsed disease: a patient who previously achieved a CR or PR, but after a period of 6 months or more demonstrates evidence of progression;

    Refractory disease: treatment failure or disease progression within 6 months of the last anti-leukemia therapy.
- Previously treated with at least one but not more than three lines of therapy (a line of therapy is defined as completing at least two cycles of treatment for a given line of therapy), including at least one prior standard chemotherapy-containing regimen according to current guidelines
- For patients with 17p deletion, previously treated with at least one but not more than three lines of therapy, including at least one prior standard chemotherapy-containing regimen according to current guidelines OR at least one prior alemtuzumab-containing therapy
- Patients previously treated with bendamustine only if their DOR was ≥24 months
- Patient requires treatment in the opinion of the investigator
- Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 1

- Adequate bone marrow function independent of growth factor or transfusion support within 2 weeks of screening, at screening as follows unless cytopenia is clearly due to marrow involvement of CLL:

  Platelet count $\geq$ 75,000/mm^3; in cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator), platelet count should be $\geq$ 30,000/mm^3

  Absolute neutrophil count (ANC) $\geq$ 1000/mm^3 unless neutropenia is clearly due to marrow involvement of CLL (per the discretion of the investigator)

  Total hemoglobin $\geq$ 9 g/dL unless anemia is due to marrow involvement of CLL (per the discretion of the investigator)

- Adequate renal and hepatic function, per laboratory reference range at screening as follows:

  Calculated creatinine clearance $\geq$ 50 mL/min using 24-hour creatinine clearance or modified Cockcroft–Gault equation (using ideal body mass [IBM] instead of mass):

$$\text{eCCr} = \frac{(140-\text{Age}) \bullet \text{IBM (kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

  Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140-\text{Age}) \bullet \text{IBM (kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/L})}$$

  (IBM) should be used:

  IBM (kg) = [(height in cm − 154) × 0.9] + (50 if male, 45.5 if female)

  AST and ALT $\leq$ 3.0 × the upper limit of normal (ULN) of the institution's normal range;

  Bilirubin $\leq$ 1.5 × ULN. Patients with Gilbert's syndrome may have a bilirubin level > 1.5 × ULN, per discussion between the investigator and the Medical Monitor;

  Prothrombin time (or international normalized ratio) and partial thromboplastin time not to exceed 1.2 × the institution's normal range (patients with an elevated prothrombin time and known lupus anticoagulant may be eligible for participation after consulting he Medical Monitor).

- Female patients must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:

  At screening, on a serum sample obtained within 14 days prior to initiation of study treatment, and

  Prior to dosing, on a urine sample obtained on the first day of study treatment if it has been > 7 days since obtaining the serum pregnancy test result.

- Female patients who are not surgically sterile or postmenopausal (for at least 1 year) must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 30 days after study treatment or 12 months after completing therapy with rituximab, whichever is later:

  Total abstinence from sexual intercourse;

  A vasectomized partner;

  Hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) that started at least 3 months prior to study drug administration;

  Double-barrier method (condom + diaphragm or cervical cup with spermicidal contraceptive sponge, jellies, or cream).

- Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 3 months after study treatment or 12 months after completing therapy with rituximab, whichever is later:

    A partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration;

    Total abstinence from sexual intercourse;

    Double-barrier method (condom + diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream).

Patients who meet any of the following criteria will be excluded from study entry:

- Transformation of CLL to aggressive non-Hodgkin's lymphoma (NHL) (e.g., Richter's transformation, prolymphocytic leukemia, or diffuse large B-cell lymphoma [DLBCL] or CNS involvement by CLL.
- Undergone an allogeneic stem cell transplant.
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia.
- History of intolerance to prior bendamustine treatment (defined as toxicity requiring permanent discontinuation of bendamustine) or other contraindication to bendamustine treatment.
- History of severe (i.e., requiring permanent discontinuation of prior rituximab therapy) prior allergic or anaphylactic reactions to rituximab.
- Known HIV positivity.
- Positive test results for chronic hepatitis B infection (defined as positive HBsAg serology)

    Patients with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly polymerase chain reaction (PCR) HBV DNA testing.

- Positive test results for hepatitis C (HCV antibody serology testing)

    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Requires the use of warfarin (due to potential drug – drug interactions that may potentially increase the exposure of warfarin). Patients may be eligible if able to be taken off warfarin and started on an alternative anticoagulant.
- Received an anti-CLL monoclonal antibody within 8 weeks prior to the first dose of study treatment
- Received any of the following agents within 28 days prior to the first dose of study treatment:
- Any anti-cancer therapy including chemotherapy or radiotherapy and steroid therapy for anti-neoplastic intent, investigational therapy, including targeted small-molecule agents
- Has not recovered to less than Grade 2 clinically significant adverse effect(s)/toxicity(ies) of any previous therapy
- Received potent CYP3A4 inhibitors (such as fluconazole, ketoconazole, and clarithromycin) within 7 days prior to the first dose of study treatment
- Received potent CYP3A4 inducers (such as rifampin, carbamazepine, phenytoin, St. John's wort) within 7 days prior to the first dose of study treatment
- History of prior venetoclax treatment.
- Consumed grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of study drug
- A cardiovascular disability status of New York Heart Association Class ≥ 3. Class 3 is defined as cardiac disease in which patients are comfortable at rest but marked limitation of physical activity due to fatigue, palpitations, dyspnea, or anginal pain.
- A significant history of renal, neurologic, psychiatric, endocrine, metabolic, immunologic, cardiovascular, or hepatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes.

- Major surgery within 30 days prior to the first dose of study treatment
- A patient who is pregnant or breast-feeding
- History of prior other malignancy that could affect compliance with the protocol or interpretation of results with the exception of the following:

  Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study

  Other cancers not specified above which have been curatively treated by surgery and/or radiation therapy from which patient is disease-free for ≥5 years without further treatment
- Malabsorption syndrome or other condition that precludes enteral route of administration
- Known allergy to both xanthine oxidase inhibitors and rasburicase
- Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal)
- Vaccination with a live vaccine within 28 days prior to randomization

Length of Study

The approximate length of the study will be 56 months, based on an enrolment period of 20 months and the end of study as defined below.

End of Study

The end of the study will be approximately 3 years after last patient is enrolled allowing for completion of the maximum duration of planned therapy (in the absence of disease progression) as well as at least 1 year of follow-up for all patients.

Efficacy Outcome Measures

Primary Efficacy Outcome Measures

The primary efficacy outcome measure for this study is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse, determined using standard iwCLL guidelines, or death from any cause, whichever comes first.

While the primary efficacy endpoint is investigator-assessed PFS, PFS based on IRC assessments will also be analyzed to support the primary analysis. In the United States, IRC-assessed PFS will be the basis for regulatory decisions.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- IRC-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory
- Investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory
- Best OR (defined as CR, CRi, nPR, and PR)rate as assessed by the investigator
- OR CR, CRi, nPR, and PR rates at end of combination treatment response visit, as assessed by the investigator. Disease response will be assessed according to the iwCLL guidelines
- OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit, as assessed by the IRC
- OS, defined as the time from randomization to death from any cause
- EFS, defined as the time between randomization and the date of disease progression/relapse, death from any cause, or start of a new anti-therapy
- DOR, defined for patients with a best OR of CR, CRi, *nPR,* or PR as the time from first occurrence of a *CR,* CRi, nPR, or PR to disease progression/relapse, as assessed by the investigator, or death from any cause.
- TTNT, defined as the time from randomization to start of new non-protocol anti-CLL therapy or death from any cause.

- MRD response rate (determined as the proportion of patients with MRD negativity) at End of Combination Treatment Response Visit as measured at a central laboratory on peripheral blood and/or bone marrow samples.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events and serious adverse events
- Changes in clinical laboratory results (including hematology and chemistry) during and following administration of study treatment
- Incidence of adverse events of special interest:

  Grade > 3 TLS and infusion-related reactions (IRRs)

  Measures of immune function, including serial immunoglobulin levels (IgG, IgM, IgA) following treatment with venetoclax+R or BR.

Pharmacodynamic Outcome Measure

The pharmacodynamic outcome measure for this study is as follows:

- Serial assessment of B- and T-cell lymphocyte subsets by flow cytometry.

Pharmacokinetic Outcome Measures

The PK outcome measures for this study include:

- Plasma venetoclax concentrations at the specified timepoints
- Apparent clearance, apparent volume of distribution, and other appropriate PK parameters of venetoclax characterized using population PK techniques, as data allow.

Patient-Reported Outcome Measures

The PRO outcome measures for this study are as follows:

- MDASI
- EORTC QLQ-C30 and QLQ-CLL16

Health Economic Outcome Measure

The health economic outcome measure for this study is as follows:

- The EQ-5D questionnaire.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Evaluation of the relationship between response and PFS and various potential biomarkers, including Bcl-2 expression, for patients treated with venetoclax+R or BR.
- Assessment of potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with venetoclax+R or BR.
- MRD response rate as measured at a central laboratory on peripheral blood samples and/or bone marrow aspirate samples at the disease response assessment timepoints

Investigational Medicinal Products

Test Product

Arm A: Venetoclax and Rituximab (venetoclax+R)

Venetoclax tablets will be administered daily orally, starting with a daily dose of 20 mg on Day 1 of the venetoclax dose ramp-up period, followed by 50 mg daily from Day 8, followed by 100 mg daily from Day 15, followed by 200 mg daily from Day 22, followed by 400 mg daily from Day 29. Venetoclax will then be self-administered at 400 mg per day for a maximum of 2 years from Cycle 1, Day 1 or until disease progression (whichever is earlier). Combination therapy

consisting of 6 cycles of rituximab and daily venetoclaxdosing will start after completion of the venetoclaxramp-up period.

Rituximab will be administered intravenously at a dose of 375 mg/m^2 on Day 1 of Cycle 1 followed by 500 mg/m^2 IV on Day 1 of Cycles 2 through 6.

Comparator

Arm B: Bendamustine and Rituximab (BR)

Bendamustine will be administered at 70 mg/m^2 IV on Days 1 and 2 of Cycles 1 through 6.

Rituximab will be administered at 375 mg/m^2 IV on Day 1 of Cycle 1 and 500 mg/m^2 IV on Day 1 of Cycles 2 through 6.

Non-Investigational Medicinal Products

Permitted Concomitant Therapy and Clinical Practice

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use for the duration of the study or at least 30 days after the last dose of study drug or one year after the last dose of rituximab, whichever is longer.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin) if clinically indicated. Granulocyte colony-stimulating factor (G-CSF) may be administered as primary prophylaxis in each cycle of therapy, as per the American Society of Clinical Oncology (ASCO) guidelines or each site's institutional standards.

Anti-emetic therapy may be instituted for any patient if clinically indicated. Bendamustine has a moderate risk of emesis. It is recommended that bendamustine infusions be administered following premedication with a serotonin (5-HT3) antagonist (i.e., dolasteron, ondansetron, etc.) or as per institutional practice.

Systemic steroid therapy will not be allowed either during or within 7 days prior to the first dose of study treatment with the exception of inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease (COPD), single infusions of hydrocortisone prior to rituximab infusions, topical steroids, or replacement corticosteroid therapy for an inherited or acquired deficiency.

Premedication before rituximab infusion:

- Oral acetaminophen/paracetamol (650–1000 mg) at least 30 minutes prior to the start of infusion (mandatory for all infusions)
- Antihistamine such as diphenhydramine (25–50 mg) approximately 30 minutes prior to the start of the first infusion for all subsequent infusions unless previous antibody infusions did not result in an IRR > NCI CTCAE Grade 1 and there was no interruption to the infusion.
- A single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered with rituximab if this is the usual practice at the site.

Prophylaxis and Management of Tumor Lysis Syndrome (TLS)

Clinical data from CLL patients treated to date with venetoclax suggest that patients with baseline lymph nodes $\geq$ 5 cm diameter are at a greater risk for TLS than those with baseline lymph nodes less than 5 cm. In addition, the data showed that creatinine clearance of $\leq$ 80 mL/min at screening was a secondary risk factor for TLS. On the basis of the data review performed by the Sponsors, the following are three TLS risk categories identified:

1. **TLS low-risk category**: the presence of all measurable lymph nodes with the largest diameter $<$ 5 cm by radiographic assessment AND absolute lymphocyte counts $< 25 \times 10^9$/L.
2. **TLS medium-risk category**: the presence of all measurable lymph nodes with the largest diameter $\geq$ 5 cm and $<$ 10 cm by radiologic assessment OR absolute lymphocyte count $\geq 25 \times 10^9$/L.
3. **TLS high-risk category**: the presence of any lymph node with the largest diameter $\geq$ 10 cm by radiologic assessment OR the presence of BOTH an absolute lymphocyte count $\geq 25 \times 10^9$/L AND a measurable lymph node with the largest diameter $\geq$ 5 cm by radiologic assessment.

All patients enrolling in the study will be assessed at screening and categorized in a TLS risk category as described above.

Initial Doses: 20 and 50 mg

All patients, irrespective of their TLS risk category, must receive the following TLS prophylaxis measures prior to the initiation of the first doses of venetoclax:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax and rituximab is completed
- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to the start of treatment and continued for at least 24 hours after the first dose
- Serum chemistry and hematology laboratory samples must be drawn anytime within 72 hours prior to first dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax. If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, first dose of venetoclax must be delayed until resolution and management per the protocol, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome, must be initiated. If active correction of electrolytes was performed, the first dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

TLS Low Risk

Low-risk patients will receive their initial doses of 20 and 50 mg as outpatients.

For patients unable to maintain oral hydration at 1.5–2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from “before dosing” laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

Medium-risk patients who have creatinine clearance ≥ 80 mL/min will receive their initial doses of 20 and 50 mg as outpatients. Patients with creatinine clearance < 80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator) may be handled as High-Risk patients (see the High Risk section for details of hydration, laboratory, etc.).

In addition to oral hydration stated above, IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion

TLS High Risk

High-risk patients will be hospitalized to receive their initial doses of 20 and 50 mg. Hospitalization will begin the evening prior to each initial dose of venetoclax and continue for 24 hours after.

Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.

Rasburicase must be administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or Cairo-Bishop threshold of 476 µmol/L). For patients with a contraindication to rasburicase (i.e., glucose-6-phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines.

Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

Serum chemistry, hematology, and vital signs will be performed before dosing and at 4 (serum chemistry only), 8, 12 (serum chemistry only), and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour post-dose laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug. Additional laboratory assessments may be performed per investigator discretion.

Subsequent Dose Increases during the Venetoclax Ramp-Up Period: 100, 200, and 400 mg

All patients, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to subsequent dose increases of venetoclax:

- Continued administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged at subsequent dose increases for patients unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

- Serum chemistry and hematology laboratory samples must be drawn within 72 hours prior to dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to each dose increase of venetoclax, or the patient should receive additional prophylactic treatment prior to dosing. If clinically significant laboratory abnormalities are observed in this laboratory assessment, dose of venetoclax must be delayed until resolution, and management per the protocol, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome, must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing. If active correction of electrolytes was performed, the first or subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

TLS Low Risk

Low-risk patients will receive the subsequent dose increases (100, 200, and 400 mg) as outpatients.

Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and at 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from “before dosing” laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

Medium-risk patients who have creatinine clearance ≥ 80 mL/min will receive their subsequent dose increases as outpatient. Patients with creatinine clearance < 80 mL/min and/or who have high tumor burden (defined per the discretion of the investigator) may be hospitalized.

For patients who receive this subsequent dose increases as outpatient, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from “before dosing” laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 4, 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate for patients who are hospitalized.

TLS High Risk

High-risk patients with creatinine clearance of ≥ 80 mL/min will receive the subsequent dose increases as outpatients. Patients with creatinine clearance < 80 mL/min and/or high tumor burden (defined per the discretion of the investigator) may be hospitalized. Hospitalization will begin the evening prior to the dose of venetoclax and continuing for 24 hours after.

IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.

For patients not hospitalized, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be performed before dosing and 4, 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

Additional laboratory assessments may be performed per investigator discretion.

Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose held until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome. If active correction of electrolytes was performed, the first dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours. If venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). Dose must be resumed at one lower dose level if interruption lasted more than 7 days. All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose.

First Rituximab Dose

All patients will have the following procedures regardless of TLS risk category:

The first dose of rituximab will be given in an outpatient setting. Patients may be hospitalized for the first dose of rituximab at the investigator's discretion following discussion with the Medical Monitor.

Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged for patients unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.

Venetoclax will be taken at least 30 minutes prior to starting the rituximab infusion.

Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing of venetoclax. Laboratory samples should be sent and analyzed immediately. Results from predose laboratory values are not required to be available prior to initiating venetoclax treatment provided laboratory values obtained within 24 hours before dosing were within normal limits. The 8-hour laboratory results must be reviewed prior to the patient leaving the clinic.

The 24-hour chemistry values must be reviewed before the patient receives the next day dose of venetoclax. If there is no evidence of TLS 24 hours after rituximab and venetoclax dose, patients can continue on venetoclax daily dosing.

Patients who develop any electrolyte changes suggestive of TLS should have his or her subsequent venetoclax dose held until the electrolyte abnormalities resolve, undergo aggressive management and further monitoring per Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome. If active correction of electrolytes was performed, the first dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.

Downgrading TLS Risk Category

Patients classified as TLS high-risk at screening due to an absolute lymphocyte count $\geq 25 \times 10^9$/L AND a measurable lymph node with the largest diameter $\geq$ 5 cm but less than 10 cm by radiologic assessment may have a re- evaluation of their TLS risk category based on their most recent ALC for dose increases above 50 mg. Based on those results, one of the following two options may be implemented:

If the patient's ALC decreases to $< 25 \times 10^9$/L, the patient may be categorized as TLS medium-risk and follow the management guidelines for the TLS medium-risk category for subsequent dose increases (to 100, 200, 400 mg) of venetoclax during the Ramp-Up Period.

If the patient's ALC remains $\geq 25 \times 10^9$/L, the patient will remain in the TLS high-risk category and continues to follow management guidelines for TLS high-risk patients for subsequent dose increases of venetoclax during the Ramp-Up Period. Re-assessment of the patient's TLS risk category can occur prior to each subsequent dose increase.

Statistical Methods

Primary Analysis

Efficacy

The primary efficacy endpoint is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard iwCLL guidelines), or death from any cause, whichever comes first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of the last disease assessment. If no disease assessments were performed after the baseline visit, PFS will be censored at the time of randomization + 1 day. Although the primary efficacy endpoint is investigator-assessed PFS, PFS based on IRC assessments will also be analyzed to support the primary analysis. In the United States, IRC-assessed PFS will be the basis of regulatory decisions.

Treatment comparison will be made using a two-sided stratified log-rank test (0.05 significance level, appropriately adjusted for an interim analysis) stratified by 17p deletion status (yes or no), risk status (high or low risk),and geographic region (United States/Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America). If the null hypothesis is rejected and the observed hazard ratio is favorable for the venetoclax+R combination, then it is shown that venetoclax+R has significantly longer PFS than BR.

If the study meets its primary endpoint of prolonging PFS assessed by the investigator in all randomized patients, then formal statistical tests of *specific key secondary efficacy endpoints will be performed.* To adjust for multiple testing of the primary and key secondary efficacy endpoints, thereby controlling the overall type I error rate at a 2-sided significance level of 0.05, a fixed sequence testing procedure will be used. *Additional secondary endpoints will not be tested formally. Further details of the fixed sequence testing will be described in the Statistical Analysis Plan.*

Secondary efficacy outcome measures include:

- *Investigator-assessed PFS in patients with 17p deletion per central laboratory FISH test*
- *IRC-assessed PFS in patients with 17p deletion per central laboratory FISH test*
- *Investigator-assessed best OR rate, CR, CRi, nPR, and PR rates*
- *IRC-assessed best OR rate, CR, CRi, nPR, and PR rates*
- OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit as assessed by the investigator.
- OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit, as determined by the IRC.
- *OS, defined as the time from the date of randomization to the date of death from any cause. Patients who were not reported as having died at the time of analysis will be censored at the date when they were last known to be alive as documented by the investigator.*
- EFS, defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-CLL treatment. *If the specified event (disease progression/relapse, death, start of a new anti-CLL treatment) does not occur, patients will be censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS will be censored at the time of randomization.*
- DOR, defined for patients with a best OR of CR, CRi, nPR, or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse as assessed by the investigator or death from any cause. *For patients achieving a response who have not progressed, relapsed, or died at the time of analysis, DOR will be censored on the date of last response assessment. Patients who have never had responded will not be included in this analysis.*
- TTNT, defined as the time from randomization to start of new non-protocol anti-*-CLL* therapy or death from any cause. *For patients who have not received the next anti-CLL treatment or died at the time of analysis, TTNT will be censored at the date when the patient was last known to be alive without having received additional anti-lymphoma treatment.*
- MRD response rate (determined as the proportion of patients with MRD negativity) at End of Combination Treatment Response Visit as measured at a central laboratory on peripheral blood and/or bone marrow samples

Time-to-event endpoints such as OS, EFS, and TTNT will be analyzed using the same statistical methods described for the primary analysis of PFS.

Time-to-event analysis of DOR will incorporate data only from the subset of patients in both treatment arms that achieved a CR, CRi, nPR, or PR status. As this a nonrandomized comparison, a formal statistical test will not be conducted, and the results will only be summarized by the treatment arm estimates and confidence intervals.

Response rates in the treatment groups will be compared using stratified Cochran–Mantel–Haenszel (CMH) tests. Stratification factors are identical to those used for the primary endpoint. Rates and 95% confidence intervals will be reported for each treatment group.

Safety

The safety analyses will include all randomized patients who received at least one dose of study treatment (venetoclax, rituximab, or bendamustine), with patients grouped according to the treatment actually received.

Treatment exposure will be summarized, including the number of cycles received by each patient, and the cumulative dose will be summarized by treatment arm.

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. All AEs occurring during or after the first treatment will be summarized by treatment arm and NCI CTCAE grade. In addition, all SAEs will be summarized.

Deaths reported during the study treatment period and those reported after treatment completion/discontinuation will be summarized by treatment arm.

Adverse events leading to early treatment discontinuation and early study withdrawal will be summarized by arm and reason.

Laboratory data with values outside of the normal ranges will be identified. Additionally, select laboratory data will be summarized by treatment arm and grade using the NCI CTCAE. Of note, abnormal laboratory data that are clinically significant will be reported as adverse events and summarized in the adverse event tables.

Vital signs and other physical findings will be summarized by treatment arm.

Pharmacodynamics

The exploratory pharmacodynamic biomarker analyses will include patients with at least one predose and/or one post-dose biomarker assessment, with patients grouped according to the treatment actually received.

Blood samples for biomarker assessments will be assayed using analytically qualified methods (e.g., immunohistochemistry, ELISA, quantitative real-time polymerase chain reaction, and fluorescence-activated cell sorting).

Pharmacokinetics

Individual plasma concentrations of venetoclax will be tabulated after appropriate grouping, summarized (e.g., mean, standard deviation, coefficient of variation, median, minimum, and maximum), and plotted.

Population PK methods will be used to characterize the pharmacokinetics of venetoclax in this study in conjunction with appropriate historical data. Apparent clearance, apparent volume of distribution, and other appropriate PK parameters of venetoclax may be calculated and summarized as data allow.

Potential correlations of exposure with dose, demographics, pharmacodynamic variables, safety, and efficacy outcomes may be explored as warranted by the data. The results from the population PK analysis may be reported separately from the Clinical Study Report.

At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of venetoclax.

Patient-Reported Outcomes

Scoring for the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 questionnaires will be based on their corresponding user manuals. For the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales with more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

Summary statistics of the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales and their changes from baseline will be calculated at each assessment timepoint for both study arms.

Disease-related symptom progression will be measured by EORTC QLQ-C30 and EORTC QLQ-CLL questionnaires. Time-to-event Kaplan-Meier analysis on CLL symptoms will be used to demonstrate the time from first treatment to worsening in disease-related symptoms. An event is a change in symptom score by 10 points or more as defined as being clinically important.

Health Economics

Health economic data, as assessed by the EQ-5D, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D assessment that generate a score. Scores at baseline and change from baseline scores for each timepoint will be quantified using descriptive statistics.

Determination of Sample Size

The primary endpoint of PFS was used to determine the sample size for the study. Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Two-sided log-rank test at the 0.05 level of significance
- 80% power to detect a hazard ratio (HR) for venetoclax + R versus BR of 0.66, corresponding to an approximate median improvement of 15.2 months to 23 months (34% reduction in risk of a PFS event)
- Exponential distribution of PFS
- An annual dropout rate of 5%
- One interim analysis for efficacy

With these assumptions, 186 PFS events are required to achieve 80% power for the primary analysis of PFS in all patients for detecting a trend in favor of venetoclax + R arm over BR arm (HR $\leq$ 0.66). In total, it is planned to enroll approximately 370 patients across 2 arms, randomized with 1:1 ratio. It is expected that, after a 9-month enrollment ramp-up, 24 patients per month will be recruited, and the total enrollment is expected to take approximately 20 months.

Interim Analyses

An interim analysis is planned when approximately 140 investigator-assessed PFS events or deaths have occurred in both treatment arms combined (75% of the 186 events required for the final primary efficacy analysis).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
ASCT	allogeneic stem cell transplantation
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
AST	aspartate aminotransferase
AUC	area under the concentration – time curve
AUC_{0-24}	area under the concentration – time curve from time 0 to 24 hours post-dose
BCRP	breast cancer resistance protein
BR	bendamustine and rituximab
BSA	body surface area
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	chronic lymphocytic leukemia
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CRO	contract research organization
CT	computed tomography
CTLS	clinical tumor lysis syndrome
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer

Abbreviation	Definition
ePRO	electronic patient-reported outcome
EQ-5D	EuroQol 5 Dimension
ESMO	European Society for Medical Oncology
FC	fludarabine and cyclophosphamide
FCR	fludarabine, cyclophosphamide, rituximab
FDA	U.S. Food and Drug Administration
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FR	fludarabine, rituximab
G-CSF	granulocyte colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVcAB	hepatitis C virus core antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hazard ratio
HRQoL	health-related quality of life
IBM	ideal body mass
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous
IVRx	interactive voice response solution
iwCLL	international workshop on Chronic Lymphocytic Leukemia
IxRS	interactive voice/Web-based system
LTLS	laboratory tumor lysis syndrome
LVEF	left ventricular ejection fraction
MDASI	M. D. Anderson Symptom Inventory
MDS	myelodysplastic syndrome

Abbreviation	Definition
miRNA	microRNA
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-WG	National Cancer Institute Working Group
NHL	non-Hodgkin's lymphoma
nPR	nodular partial response
OATP1B1	organic anion transporter protein 1B1
OATP1B3	organic anion transporter protein 1B3
OCT1	organic cation transporter 1
OR	overall response
OS	overall survival
P-gp	P-glycoprotein 1
PCR	polymerase chain reaction
PD	progressive disease
PE	polyethylene
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PUR	polyurethane
PVC	polyvinyl chloride
QD	once daily
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-CLL16	Quality of Life Questionnaire CLL module
QOL	quality of life
ROW	rest of world
RCR	Roche Clinical Repository
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease

Abbreviation	Definition
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
STD	severely toxic dose
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
TTNT	time to next anti-CLL treatment
ULN	upper limit of normal
USPI	United States Product Insert

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most common of the chronic leukemias, comprising 30% of all adult leukemias, with a median age at diagnosis of 72 years. CLL is a clonal disease of unknown etiology, characterized by the accumulation of mature B cells in blood, lymph nodes, spleen, liver, and bone marrow.

Morphologically, CLL cells are relatively mature appearing but immunologically incompetent. About 95% of CLL is of B-cell origin (B-CLL) with a characteristic phenotype (CD5+, CD23+; weak surface expression of CD19, CD20, and CD79b; and IgM- or IgD-restricted). Chromosomal abnormalities of the leukemia cells are found in >80% of cases, with the most common being deletion 13q14 (incidence 55%), deletion 11q- (18%), trisomy 12 (16%), and deletion 17p (7%) (Döhner et al. 2000).

More than 50% of CLL patients are asymptomatic at diagnosis and require no treatment. Symptoms appear as the disease progresses. Treatment is initiated when a patient's disease becomes symptomatic or progressive as defined by the international workshop on Chronic Lymphocytic Leukemia (iwCLL)'s updated guidelines for diagnosis and treatment of CLL (Hallek et al. 2008).

Response rates to initial treatment are high, but relapsed or refractory disease is often characterized by resistance to chemotherapy (i.e., fludarabine or alkylating agents). Relapsed disease is associated with a median survival between 15 and 44 months and is dependent of CLL risk status, time to relapse, and choice of regimen (Lamanna et al. 2006; Wierda et al. 2010; Badoux et al. 2011; Fischer et al. 2011). Rituximab is approved for the treatment of both previously treated and previously untreated CLL in combination with chemotherapy in Europe and with fludarabine and cyclophosphamide (FC) in the United States. Besides the regimen of FC and rituximab (FCR), the combination regimen approved in the United States, one of the more commonly used and active regimens in relapsed CLL is the combination of bendamustine and rituximab (BR). The BR regimen was demonstrated to have meaningful clinical activity in relapsed/refractory CLL patients with an observed overall response (OR) rate of 59% and a median progression-free survival (PFS) of 15.2 months (Fischer et al. 2011).

Despite recent progress, CLL remains incurable; therefore, there is a need for the development of new treatments that could improve both response rate and the survival of these patients.

1.2 BACKGROUND ON VENETOCLAX (GDC-0199*)*

1.2.1 Bcl-2 Protein Family

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma (FL), where the t(14;18)

chromosomal translocation results in significant overexpression of Bcl-2 protein in B cells. The Bcl-2 family of genes encodes a group of closely related proteins that exhibit pro- or anti-apoptotic activity and share up to four Bcl-2 homology domains (Korsmeyer 1999; Cory and Adams 2002; Borner 2003; Cory et al. 2003). Bcl-2 overexpression is a major contributor to the pathogenesis of several lymphoid malignancies and is overexpressed in acute and chronic leukemias.

In CLL cells, the microRNAs (miRNAs) miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2 (Calin et al. 2008). Although Bcl-2 expression levels are variable across patients, high expression of Bcl-2 (compared with normal white blood cells) is observed in CLL cells in ≥95% of CLL patients (unpublished data from Phase II study of ABT4710n [navitoclax]).

Bcl-2 overexpression represents one common mechanism for evading apoptosis. However, CLL cells may concurrently express high levels of Bcl-2 prebound to pro-death proteins such as Bim, thus priming these cells for death such that treatment with a BH3 mimetic like venetoclax will rapidly drive them into apoptosis (Del Gaizo Moore et al. 2007; Del Gaizo Moore and Letai 2008). Nonclinical data in non-Hodgkin's lymphoma (NHL) cell lines support a model analogous to CLL, where higher levels of Bcl-2 expression correlate strongly with greater sensitivity to venetoclax (unpublished data, [redacted] CLL and many NHL cells are therefore dependent on high levels of Bcl-2 for survival, making them potentially attractive targets for venetoclax. Furthermore, this sensitivity to Bcl-2 inhibition may provide the possibility for a chemotherapy-sparing option for CLL patients.

1.2.2 Venetoclax

1.2.2.1 Venetoclax Nonclinical Activity and Pharmacokinetic Profile

Venetoclax (synonymous with GDC-0199 and ABT-199 and referred to as venetoclax throughout the protocol) is a highly selective, orally available small-molecule Bcl-2 family protein inhibitor that binds with high affinity (dissociation constant [Ki] <0.10 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-X_L and Bcl-w (>480-fold and >2000-fold lower affinity than to Bcl-2, respectively). Overexpression of anti-apoptotic Bcl-2 family proteins is associated with resistance to chemotherapy, and antagonism of the action of these proteins might overcome resistance and enhance response to therapy. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

In vitro, venetoclax demonstrated broad cell-killing activity against a panel of lymphoma and leukemia cells including B-cell FLs, mantle cell lymphomas, diffuse large B-cell lymphomas (DLBCLs), and acute myeloid leukemias (AMLs). Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell

lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than were wild-type cell lines.

Venetoclax inhibited subcutaneous murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL) and NHL.

The pharmacokinetic (PK) profile of venetoclax was evaluated in multiple animal species. In mice, rats, monkeys, and dogs, low plasma clearance and low volumes of distribution characterized the venetoclax PK profile. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs. Food had a marked effect on the oral bioavailability in dogs.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (>99.9%). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Liver metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

In vitro, venetoclax is metabolized by CYP3A4. Thus, co-administration of venetoclax with drugs that inhibit CYP3A4 is predicted to cause a significant increase in the exposure of venetoclax. At clinically relevant concentrations for the 400 mg once daily (QD) dose regimen, venetoclax and M27 are not predicted to inhibit or induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Venetoclax is a substrate for P-glycoprotein 1 (P-gp) and breast cancer resistance protein (BCRP). Active uptake of venetoclax or it's major human metabolite(M27) was not observed in cells overexpressing organic anion transporter protein 1B1 (OATP1B1), organic anion transporter protein 1B3 (OATP1B3), or organic cation transporter 1 (OCT1), indicating that venetoclax is not a substrate for those transporters in vitro. Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor in vitro.

M27 are not predicted to inhibit or induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

See the Venetoclax Investigator's Brochure for a detailed discussion of the nonclinical activity of venetoclax.

1.2.2.2 Venetoclax Nonclinical Toxicology

Venetoclax has been assessed in repeated-dose general toxicology studies and in genetic, developmental/reproductive, and safety pharmacology studies.

Repeated-dose oral toxicity studies with venetoclax were conducted in mice and dogs. GLP-compliant definitive toxicity studies consisted of IND-enabling studies in mice and dogs with 4 weeks of dosing followed by a 4-week (dose-free) recovery period; a 2-week

toxicity study in dogs that focused on lymphocyte recovery over an extended (18 weeks) recovery period; and chronic toxicity studies in mice (6 months) and dogs (9 months). No recovery periods were included in the chronic toxicity studies. The maximum venetoclax plasma exposures (mean AUC0-24 h) achieved in the 4-week studies were 92 µg•hr/mL (at 600 mg/kg/day) in mice and 572 µg•hr/mL (at 150 mg/kg/day) in dogs. In the chronic toxicity studies, AUCs reached 34.1 µh•h/mL (at 300 mg/kg/day) in mice and 85.6 µh•h/mL (at 20 mg/kg/day) in dogs. In addition, repeat-dose toxicity studies (with no recovery periods) were conducted in wild-type variants of the Tg.rasH2 mouse strain and in Sprague-Dawley rats to select dosages for possible carcinogenicity assessments.

The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice, rats, and dogs; the male dog reproductive system (testicular germ cell depletion); and embryofetal toxicity in mice.

Venetoclax produced robust, generally dose-related decreases in lymphocytes in the peripheral blood (up to −75% in mice, − 64% in rats, and −81% in dogs) and in lymphoid tissues. In dogs, the recovery of lymphocyte counts (total lymphocytes, CD4+ and CD8+ T cells and mature B cells) was prolonged, requiring up to 18 weeks after completion of 2 weeks of dosing. B cells were the most sensitive lymphocyte subtype based on the magnitude of decrease and/or the length of time required for recovery (i.e., 25%−111% of individual baseline; mean reversal to 54% of baseline average). T−cell subsets reversed more readily and showed more dose-dependence in recovery time and extent. Decreases of lymphocytes in lymphoid tissues were reversible in mice and reversible to partially reversible in dogs. Venetoclax-related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically-mediated and non-adverse.

In the 4-week mouse and dog studies, dose-related reversible decreases in RBC mass were observed. Effects on RBC mass were typified by hemoglobin decreases. At the highest dosages administered, decreases in hemoglobin reached − 21% in mice at 600 mg/kg/day and − 23% in dogs at 150 mg/kg/day and were considered to be adverse based on a criterion of -20% decrease. In rats, decreases in hemoglobin were more severe than in mice and dogs at comparable exposures and reached − 30% to − 49% at ≥ 150 mg/kg/day. Hematologic parameters (lymphocyte counts and RBC mass) are readily monitored in clinical study subjects.

No effects of venetoclax have been identified in female reproductive tissues in mice or dogs in general toxicology studies. However, in dogs, venetoclax produced adverse, non-reversible, non-dose-related microscopic findings of testicular germ cell depletion at all dosages tested; there were no testicular effects in mice or rats. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to

venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis (Olderied et al. 2001; Sugiyama et al. 2001; Yan et al. 2003).

Venetoclax resulted in increased postimplantation loss and decreased fetal body weights in the mouse embryofetal development study at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect level (NOAEL) was defined at the mid-dose of 50 mg/kg/day. Venetoclax was not teratogenic, and there were no other effects on development or fertility.

Venetoclax produced loss of hair pigmentation in dogs (reversibility has not been assessed). Evidence from Bcl-2 knockout mouse (Bcl-2 $^{-/-}$) studies indicates that hair hypopigmentation is consistent with the pharmacological effect of Bcl-2 functional loss, and occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival. A dedicated physical examination of the skin and extensive ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly, the iris and fundus) of the dog appears unaffected and was confirmed by histopathology.

Other effects of venetoclax included single cell necrosis in various epithelial tissues in dogs (i.e., gallbladder, stomach, exocrine pancreas, and epididymides). These changes were minimal except for non–dose-dependent, minimal to mild, single-cell necrosis in the pylorus of the stomach at ≥ 2 mg/kg/day in the 9-month study. After 4 weeks of dosing and a 4-week recovery period, reversibility was observed in the gallbladder and exocrine pancreas, but minimal, single-cell necrosis was still present in the epididymides and prostate (potentially related to the testicular effects) and in the stomach. Single-cell necrosis was considered not to be adverse due to its minimal-to-mild magnitude and because no loss of mucosal integrity was observed microscopically.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax.

Venetoclax was tested in a battery of safety pharmacology assays and produced no effects in CNS/neurobehavioral or respiratory studies in mice at oral doses up to 600 mg/kg. In dogs, mild reductions in cardiac contractility and cardiac output were observed at plasma concentrations of ≥16 µg/mL; these concentrations exceeded the concentration of venetoclax in humans (3.39 µg/mL at the 900-mg dose). No effects on blood pressure, heart rate, or ECG parameters were observed in dogs at a maximum drug concentration of 46 µg/mL.

See the Venetoclax Investigator's Brochure for details on the nonclinical studies.

1.2.2.3 Venetoclax Clinical Experience

As of 3 February 2014, 267 patients have received venetoclax either as monotherapy or in combination with other agents across different trials for multiple oncology indications. Five ongoing studies have enrolled 160 patients with relapsed/refractory CLL/small lymphocytic lymphoma (SLL) (95 patients in M12-175, 38 patients in M13-365, 17

patients in M13-982, 8 patients in GP28331, and 2 patients in GO28440). The first–in-human venetoclax monotherapy dose-escalation study (Study M12-175) is ongoing in patients with relapsed or refractory CLL/SLL and NHL. Study M13-365 (venetoclax in combination with rituximab in relapsed/refractory CLL), Study M13-982 (venetoclax monotherapy in relapsed/refractory CLL harboring 17p deletion), Study GP28331 (venetoclax in combination with obinutuzumab), and Study GO28440 (venetoclax in combination with bendamustine plus rituximab) are also ongoing. Preliminary safety, PK, and efficacy data are summarized below on the basis of data cutoff dates of 3 February 2014 for safety listings (see the Venetoclax Investigator's Brochure for details on clinical studies). Dose-limiting toxicity (DLT) assessments are available for patients enrolled in Study M12-175 (through Cohort 8 with a target venetoclax dose of 1200 mg) and in Study M13-365 (through Cohort 5 with a target venetoclax dose of 600 mg).

Study M12-175 includes relapsed/refractory CLL/SLL and NHL patients with measurable disease, Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1, and adequate marrow function who are enrolled in Arm A (CLL/SLL) or Arm B (NHL). Patients receive a single dose of venetoclax on Day -7 followed by continuous QD dosing from Day 1 until progressive disease (PD) or unacceptable toxicity.

Study M13-365 includes relapsed/refractory CLL patients with measurable disease, ECOG Performance Status ≤ 1, and adequate bone marrow function. Patients received venetoclax starting at 50 mg/day and were dose-escalated to the target cohort dose of venetoclax over 3 weeks followed by continuous daily dosing of venetoclax at the target cohort dose until disease progression. Rituximab was administered starting on Week 4 Day 1 at 375 mg/m^2 (the dose could be split over Cycle 1 Days 1 and 2 at the discretion of the investigator) followed by subsequent administrations of rituximab at 500 mg/m^2 on Day 1 of Weeks 5, 6, 10, 14, 18, 22, and 26.

Study M13-982 includes relapsed or refractory CLL patients harboring the 17p deletion. The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in patients with relapsed or refractory CLL harboring the 17p13 (TP53 locus) deletion (17p deletion). Efficacy will be measured by OR rate. The secondary objectives are to evaluate the CR, partial response PR, duration of response (DOR), PFS, time to progression, overall survival (OS) and percent of patients who move on to stem cell transplant. Patients will receive venetoclax orally QD continuously. To mitigate the risk for TLS, a lead-in period (up to 5 weeks) is employed to evaluate a step-wise dose escalation. Patients start with 20 mg of venetoclax on Week 1 Day 1 and, if no significant findings occur, receive 50 mg venetoclax QD for the remainder of Week 1. After 1 week at 50 mg, the dose is increased weekly first to 100 mg, then 200 mg, then 400 mg (or additional lead-in steps to designated 400-mg dose), as tolerated. A lower starting dose and/or modification to the lead-in regimen may be implemented for individuals at particularly high risk for TLS.

Study GP28331 is an open-label, dose-finding and safety study of venetoclax in combination with obinutuzumab in relapsed/refractory and previously untreated CLL patients. Venetoclax is administered in escalating doses over 2 to 5 weeks with target doses of venetoclax ranging from 100 mg/day to 600 mg/day. Patients receive 6 cycles of obinutuzumab (28-day cycles). Obinutuzumab infusions occur on Days 1, 2, 8 and 15 of Cycle 1 and on Day 1 of Cycles 2 to 6. Following completion of 6 cycles of combination therapy, patients will continue on venetoclax as a single agent at the target venetoclax dose to which they were assigned until disease progression or end of study (whichever occurs first). Following completion of the dose-finding stage in each patient population (relapsed/refractory and previously untreated CLL), a dose and schedule will be selected for use in the expansion stage of the study. The expansion stage for each patient population will have at least 14 patients.

Study GO28440 is an open-label, dose-finding and safety study of venetoclax in combination with BR in relapsed/refractory and previously untreated patients with CLL. Venetoclax is administered in escalating doses over 2 to 5 weeks with target doses of venetoclax ranging from 100 mg/day to 600 mg/day. Rituximab is administered IV once every 28-day cycle for up to 6 cycles. The initial dose is 375 mg/m^2 in Cycle 1, followed by 500 mg/m^2 in Cycles 2 to 6. Bendamustine is administered IV at 70 mg/m^2 for 2 consecutive days of each 28-day cycle for 6 cycles in patients with relapsed/refractory CLL, and at 90 mg/m^2 in previously untreated patients with CLL. Following completion of 6 cycles of combination therapy, patients will continue on venetoclax as a single agent at the target venetoclax dose to which they were assigned until disease progression or end of study (whichever occurs first). Following completion of the dose-finding stage in each patient population (relapsed/refractory and previously untreated CLL), a dose and schedule will be selected for use in the expansion stage of the study. The expansion stage for each patient population will have at least 14 patients.

See the Venetoclax Investigator's Brochure for more details on these and additional studies

1.2.2.3.1 Preliminary Safety Data Summary

This section summarizes safety events observed in patients with relapsed/refractory CLL/SLL enrolled in Studies M12-175, M13-365, M13-982, GP28331, and GO28440. See the Venetoclax Investigator's Brochure for details. A detailed description of laboratory and clinical tumor lysis syndrome (TLS) events is presented in Section 1.2.2.3.2.

Data on venetoclax and human pregnancy or venetoclax and drug abuse/drug dependency are not available.

Study M12-175

Preliminary safety data as of 3 February 2014 for 95 patients with CLL/SLL enrolled in Study M12-175 study are summarized below. The data include patients treated at dose-escalation cohorts with target doses from 50 to 1200 mg of venetoclax.

The most common adverse events, occurring in > 10% of patients, were diarrhea (38.9%), neutropenia (37.9%), nausea (34.7%), upper respiratory tract infection (30.5%), fatigue (27.4%), and cough (20%). The most common Grade 3 and above adverse events were neutropenia (34.7%) and anemia (10.5%). The most frequently reported (> 10%) adverse events considered possibly or probably related to venetoclax include neutropenia (34.7%), nausea (22.1%), diarrhea (24.2%), and fatigue (15.8%).

Serious adverse events were reported in 36 patients (37.9%). Those reported in more than 2 patients were febrile neutropenia (5.3%), autoimmune thrombocytopenia (3.2%), and TLS (3.2%). One serious adverse event resulted in death: a patient with an ongoing event of TLS experienced sudden death (see Section 1.2.2.3.2 for details).

A total of 6 patients (6.3%) experienced adverse events that led to death: malignant neoplasm progression (2), multi-organ failure (1), sudden death (1), small intestinal obstruction (1), and mental status changes (1).

A total of 11 patients (11.6%) experienced adverse events that led to study discontinuation. These adverse events included: thrombocytopenia, general physical health deterioration, sudden death, multi-organ failure, mental status change, esophageal adenocarcinoma, and diarrhea/vomiting.

In addition, Richter's transformation had been noted at the time of disease progression for 14 (14.7%) patients with CLL.

See the Venetoclax Investigator's Brochure for more details on these patients.

Study M13-982

In study M13-982, 15 out of the 17 patients enrolled (88.2%) reported treatment-emergent adverse events. The most common adverse events were nausea (35.3%) and neutropenia and fatigue (23.5% each). Seven (41.2%) patients experienced adverse events Grade 3 or above. The most common adverse events Grade 3 and above were anemia and neutropenia (17.6% each) and thrombocytopenia and lymphocyte count decreased (11.8% each). Seven patients (41.2%) experienced serious adverse events. Serious adverse events of anemia, febrile neutropenia, and abdominal pain upper were considered to have a reasonable possibility of being related to venetoclax. No patients experienced adverse events that resulted in venetoclax discontinuation or death.

Study M13-365

As of 3 February 2014, preliminary safety results are available for 38 patients enrolled in Study M13-365. Six patients were enrolled in Cohort 1 (designated venetoclax cohort dose of 200 mg), 10 patients were enrolled in Cohort 2 (designated venetoclax cohort dose of 300 mg), 7 patients were enrolled in each of Cohorts 3, 4, and 5 (designated venetoclax cohort doses of 400, 500, and 600 mg, respectively). Most patients (94.7%) reported at least one treatment-emergent adverse event. The most common adverse events were neutropenia (50%), nausea (42.1%), diarrhea and headache (28.9% each), cough (26.3%), and thrombocytopenia, fatigue, pyrexia, and upper respiratory tract infection (23.7% each).

Twenty-seven patients (71.1%) were reported to have Grade ≥ 3 adverse events. The most commonly reported Grade ≥ 3 adverse events occurring in more than 2 patients were neutropenia (50%), thrombocytopenia (18.4%), and anemia (10.5%). Serious adverse events were reported in 14 patients (36.8%). TLS was reported in 2 patients (5.3%), and each of the following events was reported in 1 patient (2.6%) each: febrile neutropenia, histiocytosis hematophagic, lower gastrointestinal hemorrhage, non-cardiac chest pain, pyrexia, bronchitis bacterial, influenza, lung infection, pneumonia hemophilus, rotavirus infection, infusion-related reaction (IRR), hyperkalemia, lymphoma transformation, Richter's syndrome, and pulmonary mass. Both events of TLS and individual events of bronchitis bacterial, pneumonia hemophilus, rotavirus infection, and hyperkalemia were considered to have a reasonable possibility of being related to venetoclax.

As described above, 1 patient experienced a serious adverse event of hyperkalemia in a setting of TLS that resulted in study discontinuation and death (see Section 1.2.2.3.2). Two additional patients experienced adverse events that resulted in discontinuation of venetoclax (lymphoma transformation and Richter's syndrome).

See the Venetoclax Investigator's Brochure for more details on these patients.

Study GP28331

In Study GP28331, 5 of the 8 patients who received venetoclax reported treatment-emergent adverse events. In this study, the most commonly reported adverse events related to venetoclax were diarrhea and IRR (in 3 patients each; 37.5%) and hyperphosphatemia, anemia, flatulence, pollakiuria, and fatigue (in 2 patients each; 25.0%). Hyperphosphatemia was reported as a serious event in the setting of laboratory TLS that occurred after the third dose of venetoclax in a patient who had not received obinutuzumab. The event resolved with IV hydration and discontinuation of study therapy.

Study GO28440

Two patients have been enrolled in the study and had data available. Study enrollment is continuing. No treatment-emergent adverse events have been reported in the 2 enrolled patients.

See the Venetoclax Investigator's Brochure for more details on these studies.

1.2.2.3.2 Summary of TLS Events in CLL Patients with Venetoclax

In Study M12-175, substantial antitumor activity was observed in the first 3 patients with CLL following a single dose of venetoclax of 100–200 mg. Within 24 hours, dramatic reductions in lymphocyte count (>95%) were observed in the 2 patients with pretreatment lymphocytosis, and laboratory TLS developed in all 3 patients (per Cairo-Bishop Criteria [see Cairo and Bishop 2004]; see the Venetoclax Investigator's Brochure for details regarding these patients). The TLS resolved without clinical complications in all 3 patients, and the patients were able to commence daily dosing of venetoclax at reduced doses (50–100 mg) within 7 days and later escalated to the target cohort dose of 200 mg.

Subsequently, changes to the venetoclax dose and schedule were implemented to obtain a more gradual tumor response and reduce the risk of TLS. The initial venetoclax dose was reduced to 50 mg (with the option of administering doses less than 50 mg in patients with bulky disease and lymphocytosis), and 2–3 weekly escalation steps were introduced to reach the final cohort dose. Intensified monitoring and standard TLS prophylaxis measures including hydration and treatment to prevent hyperuricemia have been mandated in all patients. In the subsequent seven cohorts, 53 patients with CLL/SLL were enrolled. In Cohort 2, 1 of 6 patients showed only laboratory (chemical) changes in potassium and phosphate. The electrolyte changes were not considered clinically significant, and the patient received venetoclax without delay or dose reduction and without clinical sequelae. In Cohort 4, a serious adverse event of clinical TLS (considered related to venetoclax) was reported after the initial dose of 50 mg venetoclax. [redacted]

In [redacted], two fatal adverse events in the setting of TLS were reported. The first death occurred in Study M13-365 within 24 hours after the patient received a first dose of 50 mg venetoclax. This patient had not yet received a dose of rituximab. The second death occurred in a patient in Study M12-175 after escalation to the 1200 mg venetoclax dose. [redacted]

Following the two fatal events in , the dose of venetoclax was reduced in all active patients to 600 mg or less. Overall, six DLTs of TLS and two DLTs of fatalities in the setting of TLS were reported in the venetoclax clinical program (Arm A of Study M12-175 and Study M13-365). Details of these events are provided in the Venetoclax Investigator's Brochure. Based on data of 77 CLL/SLL patients treated in the program up to that point, protocol amendments were then implemented in patients with CLL/SLL to include:

- Modified venetoclax dosing regimens (i.e., a reduction in the starting dose to 20 mg, implementation of a more gradual 5-step dose ramp-up of 20, 50, 100, and 200 mg up to the final dose) and with a maximum dose of 600 mg allowed.
- Guidance regarding identification of TLS risk categories:

  TLS low-risk: All measurable lymph nodes with the largest diameter <5 cm AND $<25 \times 10^9$/L absolute lymphocyte count (ALC)

  TLS medium-risk: Any measurable lymph node with the largest diameter ≥ 5 cm and <10 cm OR $\geq 25 \times 10^9$/L ALC

  TLS high-risk: Any measurable lymph node with the largest diameter ≥ 10 cm OR $\geq 25 \times 10^9$/L ALC AND any measurable lymph node with the largest diameter ≥ 5 cm but <10 cm
- Enhanced TLS prophylaxis and monitoring measures

in May 2013 and all studies globally were able to fully resume as of that time with new TLS measures in place.

The safety profile of venetoclax with regard to TLS has now been further characterized in 58 patients with relapsed/refractory CLL/SLL treated with venetoclax and who completed the monotherapy ramp-up period with the above TLS measures in place (data cutoff date 17 January 2014).

There was a marked reduction in severity and frequency of TLS per Cairo-Bishop (Cairo and Bishop 2004) and Howard definitions (Howard et al. 2011) in the analysis for these 58 patients with CLL/SLL who received venetoclax using the mentioned TLS prophylaxis and monitoring measures as compared with the findings in the 77 patients with CLL/SLL in the previous analysis.

None of the 58 patients experienced any serious (including fatal) or nonserious event of clinical TLS (CTLS) or laboratory TLS (LTLS) or had study treatment discontinued because of TLS. Eight patients (13.8%) were determined to have LTLS (per Cairo-Bishop definition) after medical adjudication: none in 13 low-risk patients, 5 in

19 medium-risk patients (26.3%), and 3 in 26 high-risk patients (11.5%). Three of the 8 patients had a nonserious Grade 1 adverse event related to an electrolyte change; no adverse event was reported in the other 5 patients. One additional high-risk patient had a serious adverse Grade 2 event of cytokine release syndrome considered to be in the TLS setting with no electrolyte changes. These findings differ from those in the previous analysis (N = 77) where 3 high-risk patients (3.9%) experienced CTLS and 16 patients (20.8%) experienced LTLS (6 in 27 medium-risk patients [22.2%] and 10 in 25 high-risk patients [40.0%]). When using the Howard definition for TLS (Howard et al. 2011), which requires both electrolyte changes to be outside the Cairo-Bishop thresholds, none of the 58 patients experienced CTLS or LTLS, whereas 3 (3.9%) and 7 (9.1%) patients experienced CTLS and LTLS, respectively, among the 77 patients with CLL/SLL in the previous analysis.

Moreover, consistent with the previous analysis, the risk of TLS with venetoclax in patients with CLL/SLL is characterized as highest when initiating venetoclax dosing and with a higher initial dose of venetoclax as well as higher in patients with a large tumor burden.

In addition, there were no adverse events of TLS identified in the period after completion of the ramp-up when patients received venetoclax monotherapy at the target dose or were dosed with combination agents in all ongoing clinical studies evaluating venetoclax in patients with CLL/SLL.

On the basis of the recent analysis, further modifications to the TLS prophylaxis measures for patients with CLL are done in this protocol amendment (see Section 4.4.1.2).

More details of TLS events associated with venetoclax are provided in the Venetoclax Investigator's Brochure.

1.2.2.3.3 Preliminary Activity in CLL/SLL Patients

Study M12-175

Preliminary efficacy data for the patients in the CLL/SLL arm of Study M12-175 are available as of 17 January 2014. A total of 93 patients were enrolled, with a median time on study of 6.1 months (range: 0–27 months). Twenty-three patients (24%) had CLL with 17p13 (TP53 locus) deletion (17p deletion), 55 subjects (59%) had fludarabine-refractory CLL, and 32 of the 42 patients with available status had unmutated IGHV. The median number of prior therapies was 4 (range: 1–11).

Seventy patients were evaluable for overall response based on the 2008 updated International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. The OR rate (complete response [CR]/CR with incomplete bone marrow recovery [CRi] + PR) was 76% (53 of 70 evaluable patients), with CR/CRi in 14 patients (20%) and PR in 39 patients (56%). This included 17 of 23 patients with unmutated IGHV (74% OR rate,

with 4 CR/CRi), 15 of 21 patients with 17p deletion (71% OR rate, with 3 CR/CRi), and 29 of 39 patients with fludarabine-refractory CLL (74% OR rate, 6 CR/CRi).

The median DOR was 20.5 months [95% CI; 13.8, -] for the 53 responding patients. At 12 months, 91% of patients with CR and 67% of patients with PR remained progression-free. Of the 14 subjects with CR/CRi, 9 were evaluated in local laboratories by flow cytometry for minimal residual disease (MRD); 5 were MRD negative and of these, 2 were IGHV unmutated, 4 were fludarabine-refractory, and 1 had 17p deletion.

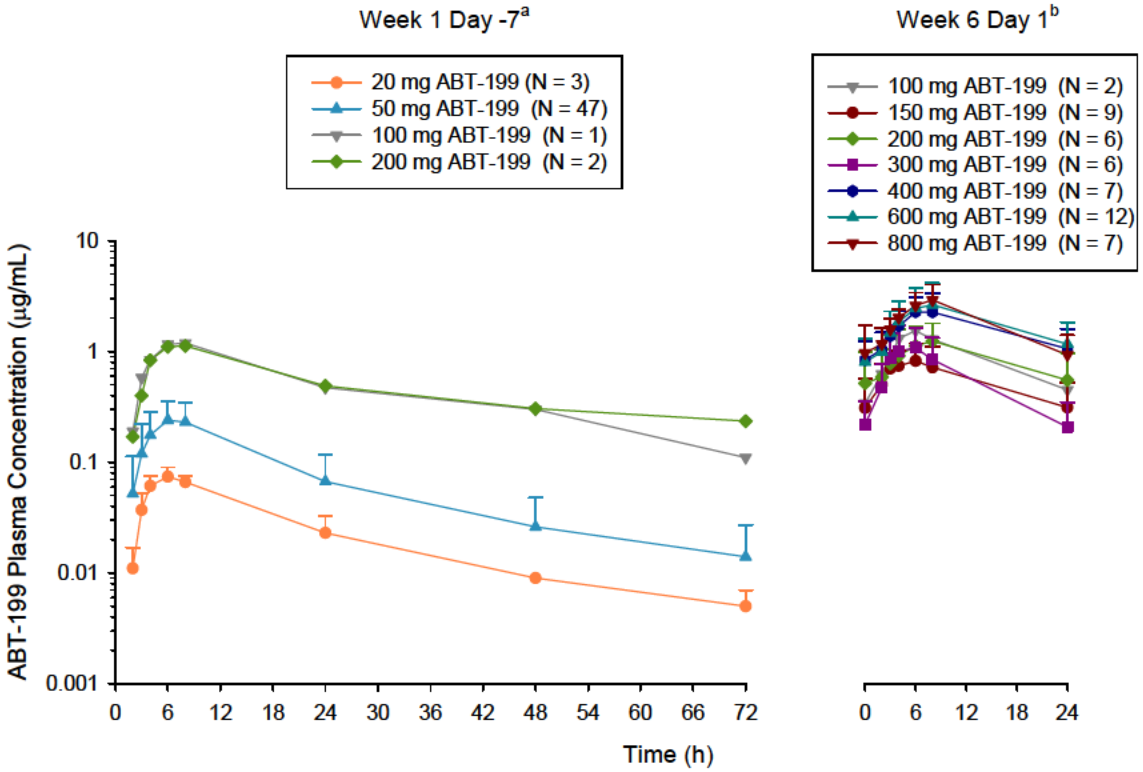
Study M13-365

Preliminary efficacy data for Study M13-365 are available as of 17 January 2014. A total of 37 patients were enrolled, with a median time on study of 4.8 months (range: 0 to 15.2 months). Nine patients (24%) had 17p deletion, 9 patients (24%) had fludarabine-refractory CLL, and 9 (24%) had rituximab-refractory CLL. The median number of prior therapies was 2 (range: 1 to 5). A total of 18 patients who completed combination therapy or discontinued prior to completion were evaluable for OR rate. The OR rate (CR/CRi+PR) was 78% (14 of 18 patients), with 7 (39%) patients achieving CR/CRi and 7 (39%) achieving PR. MRD was evaluated by local laboratory in 6 of 7 subjects with CR; 4 patients were MRD negative in the bone marrow. Of the 19 patients yet to complete combination therapy, 4 had confirmed PR, 9 have unconfirmed PR, and 6 were not yet evaluable for response.

1.2.2.4 Clinical Pharmacokinetics and Pharmacodynamics

Preliminary PK results are available from 53 patients with relapsed/refractory CLL/SLL from Study M12-175. The plasma concentration–time profiles of venetoclax in CLL/SLL patients are presented in Figure 1 following multiple doses of venetoclax at Day –7 (single dose) and Week 6 Day 1.

Figure 1 Study M12-175: Preliminary Mean (+SD) Venetoclax Plasma Concentration–Time Profiles Following Oral Administration of Venetoclax (GDC-0199 [ABT-199]) in Patients with CLL/SLL (Log-Linear Scale)



CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma.

Note: All patients were dosed under low-fat conditions.

[a] Single dose. Combined data from Week 1 Day –3 (Cohort 1) and Week 1 Day –7 (subsequent cohorts).

[b] Steady state. Combined data from Week 3 Day 1 (Cohort 1) and Week 6 Day 1 (subsequent cohorts).

In CLL/SLL patients, all venetoclax doses were orally administered after a low-fat breakfast. The absorption of venetoclax was relatively slow. Venetoclax plasma concentrations peaked at approximately 6 hours after dosing. The mean terminal phase elimination half-life of venetoclax was approximately 17 h, and the mean oral clearance was approximately 13 L/h after a single dose.

The principal pharmacodynamic effect of venetoclax is lymphocyte depletion. All of the 11 patients with CLL who had elevated lymphocyte counts pretreatment had a >50% reduction in peripheral blood lymphocyte counts after treatment (median reduction 86% [range, 59%–99%]).

CLL cells collected 6–8 hours after initial dosing of venetoclax show increased Annexin-BB staining and caspase-3 activation (Roberts et al. 2012), consistent with a mechanism of action based on Bcl-2 inhibition.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite the progress made in the treatment of patients with CLL, a significant number of patients experience relapsed disease that is associated with progressively shorter durations of response to therapy. Patients with disease that is refractory to upfront treatment are at a similar disadvantage. The only potentially curative strategy for CLL is an allogeneic hematopoietic stem cell transplantation for which the majority of patients with CLL are not eligible secondary to age or comorbid conditions. Improved treatment options are therefore critically important for this population.

Rituximab has been shown to be an effective treatment for low-grade, CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy. Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20, a hydrophobic, transmembrane protein that is present on the cell surface of pre–B lymphocytes and mature B lymphocytes but not on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissue. In particular, CD20 is present on malignant B lymphocytes in the majority of patients with mature B-cell lymphomas and leukemias. The binding of rituximab to CD20 on B lymphocytes eliminates these cells via a number of different possible mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis (Maloney et al. 2002).

Single-agent activity of rituximab with the use of a standard NHL dose has been marginal in CLL patients (Nguyen et al. 1999). However, in the past decade, more intensive doses and schedules of rituximab have been explored and demonstrated a good safety profile and significant activity in CLL (Byrd 2003; Hainsworth et al. 2003; Ferrajoli et al. 2011).

Studies in B–cell CLL patients treated with rituximab have shown a correlation with caspase activation and the depletion of B–lymphocytes, linking efficacy of this agent to activation of the intrinsic apoptotic pathway (Byrd et al. 2002). In vitro, rituximab-resistant lymphoma clones have recently been shown to up-regulate pro-survival Bcl-2 family members relative to wild-type cells and to exhibit a higher degree of resistance to numerous chemotherapeutic agents. Cutaneous B–cell lymphoma samples obtained after clinical relapse from rituximab treatment also exhibited a strong up-regulation of Bcl-2 compared with those before therapy, potentially linking anti-apoptotic Bcl-2 proteins to therapy resistance (Wobser et al. 2007). These data suggest that by lowering the apoptotic threshold, a Bcl-2 antagonist may act synergistically with rituximab in a variety of settings.

Venetoclax inhibits subcutaneous xenograft growth of human tumor cell lines derived from ALL and NHL and is highly efficacious with use of various doses and regimens. Venetoclax enhanced the activity of a broad variety of chemotherapeutic agents (e.g., cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; BR; and bortezomib) in other human hematological models (see the Venetoclax-Investigator's Brochure).

In a xenograft model of NHL (DoHH-2), venetoclax dosed as monotherapy caused significant tumor growth delay compared with the vehicle. Combining rituximab with venetoclax resulted in significantly ($p < 0.001$) improved tumor inhibition compared with venetoclax dosed as monotherapy (Genentech Report No. 10/974).

The unique mechanism of action of venetoclax suggests that it may represent a novel approach to targeting CLL. To date, the efficacy data from the single-agent Phase I dose-escalation Study M12-175 suggest that the majority of patients respond to treatment with venetoclax. Furthermore, combining venetoclax with rituximab in a chemotherapy-free regimen may be a more tolerable therapy for this generally older population.

Because TLS is a special concern in patients treated with venetoclax, intense monitoring requirements (including hospitalizations and frequent laboratory assessments) have been incorporated into this protocol; see Section 4.4.1.2 (which includes a description of patients at low, medium, and high risk for developing TLS following treatment with venetoclax), as well as Appendix 1 and Appendix 11 for monitoring guidelines.

Details regarding the safety monitoring plan for other potential risks associated with venetoclax are described in Section 5. Although the clinical experience with venetoclax in humans is limited, the safety data available to date suggest that toxicity with repeated dosing is acceptable.

Bendamustine and rituximab were selected as the comparator arm for this study because they are considered an efficacious regimen for relapsed CLL, as described in a Phase II trial of relapsed/refractory patients; specifically, patients were treated with therapies as disparate as single-agent chemotherapy and multi-agent chemoimmunotherapy (Fischer et al. 2011). There is no uniform opinion on treatment of relapsed/refractory CLL; however, BR is considered a reasonable option per the National Comprehensive Cancer Network (NCCN) guidelines, the European Society for Medical Oncology (ESMO) guidelines (Appendix 8), and a recent international consensus statement (Cheson et al. 2010). The limitations of BR include the toxicities of myelosuppression and infections (Fischer et al. 2011).

Since relapsed/refractory CLL represents an incurable disease for the majority of patients, there exists a need to introduce new agents that may improve clinical outcomes. The mechanism of action of venetoclax along with the available nonclinical and Phase I

data suggest that venetoclax may represent a more effective treatment option than current standard regimens. A treatment regimen that is demonstrated in a Phase III setting to provide a clinically meaningful increase in PFS with similar or reduced toxicity compared with BR would be considered by investigators to provide a clinically beneficial option for patients. The precautionary safety measures including the enhanced TLS risk mitigation processes in place and regular monitoring of safety in the study by an independent Data Monitoring Committee (iDMC) and by the Sponsors enables early identification of safety signals and minimizes the risk to patients enrolled. In conclusion, it is considered that the potential for benefit-risk ratio for this study is favorable.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of venetoclax and rituximab (venetoclax + R) compared with BR in patients with relapsed or refractory CLL as measured by investigator-assessed PFS

The secondary efficacy objectives for this study are as follows:

- To analyze Independent Review Committee (IRC)–assessed PFS in the subset of patients with CLL with 17p deletion identified by fluorescence in situ hybridization (FISH) testing performed at a central laboratory
- To evaluate PFS as assessed by an IRC
- To analyze investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing performed at a central laboratory
- To evaluate rate of best OR (defined as CR, CRi, nodular partial response [nPR], and PR), as assessed by the investigator
- To evaluate OR rate, CR, CRi, nPR, and PR) at end of combination treatment response visit, as assessed by the investigator
- To evaluate OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit, as assessed by the IRC
- To evaluate OS
- To evaluate event-free survival (EFS)
- To evaluate DOR for patients with a best OR of CR, CRi, nPR, or PR
- To evaluate time to next anti-CLL treatment (TTNT)
- To evaluate the proportion of patients with MRD negativity at the disease response assessment timepoints

2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the safety of venetoclax and rituximab compared with BR in patients with relapsed or refractory CLL, focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) Grade ≥3 adverse events, and Grade ≥3 laboratory toxicities

2.3 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic objective for this study is to assess changes in lymphocyte subset counts during the study (e.g., T and B cells).

2.4 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the pharmacokinetics of venetoclax in patients with relapsed or refractory CLL.

2.5 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- To compare treatment-related symptoms following treatment with venetoclax and rituximab compared with BR in patients with relapsed or refractory CLL, as measured by M. D. Anderson Symptom Inventory (MDASI) and European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and associated CLL module (QLQ-CLL16)
- To evaluate changes from baseline CLL symptoms scores with use of MDASI and EORTC QLQ-C30 and QLQ-CLL16 questionnaires
- To evaluate time to disease-related symptom progression with use of EORTC QLQ-CLL16 health-related quality of life (HRQoL) with use of global health status/quality of life (QOL) and other functional subscales of QLQ-C30
- To assess interference of treatment and disease-related symptoms on QOL with use of the MDASI questionnaire

2.6 HEALTH ECONOMIC OBJECTIVE

The health economic objective for the study is to compare the health economic effects of venetoclax in combination with rituximab versus BR in patients with relapsed or refractory CLL. The EuroQol 5 Dimension (EQ-5D) questionnaire (Rabin and deCharro 2001) will be used to support health economic/pharmacoeconomic analyses and will be analyzed post hoc.

2.7 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the relationship between efficacy outcome and potential biomarkers, including Bcl-2 expression, for patients treated with venetoclax and rituximab compared with BR

- To evaluate potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with venetoclax and rituximab or with BR

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is an open-label, international, multicenter, randomized, Phase III study to investigate the efficacy and safety of venetoclax in combination with rituximab (venetoclax+R) compared with bendamustine in combination with rituximab (BR) in patients with relapsed or refractory CLL.

Approximately 370 patients will be recruited from approximately 150 centers in up to 29 countries and randomly assigned in 1:1 ratio to receive either venetoclax+R (Arm A) or BR (Arm B). Randomization will be stratified according to the following factors:

- 17p deletion: yes or no
- Risk status: high risk or low risk

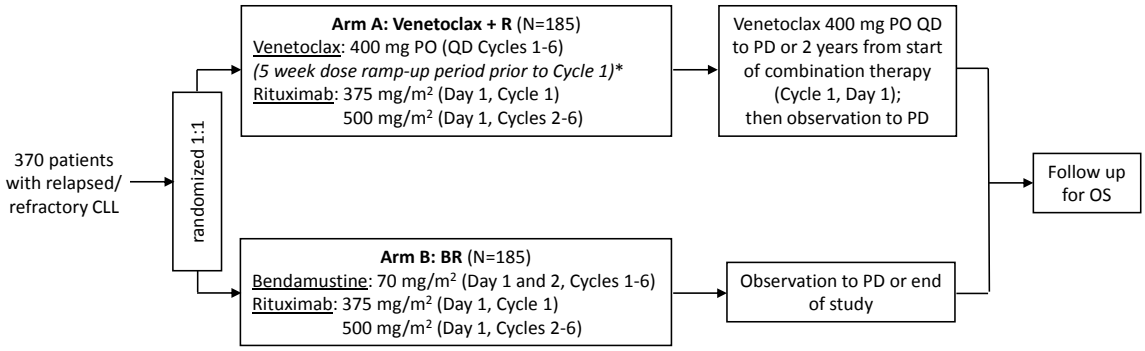
  High risk: defined as harboring 17p deletion or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy

  Low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemotherapy or chemoimmunotherapy.
- Geographic region: United States/Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America.

Patients randomized to Arm A (venetoclax+R) (see Figure 2) will have a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg daily. Following the venetoclax ramp-up period, patients will receive 6 cycles of rituximab consisting of a single infusion on the first day of each 28-day cycle. Patients will continue to take their daily dose of venetoclax during the rituximab cycles. Patients who have not progressed following the completion of the 6 cycles will continue to receive venetoclax until disease progression or for a maximum of 2 years from Cycle 1 Day 1.

Patients randomized to Arm B (BR) (see Figure 2) will receive 6 cycles of BR consisting of a single infusion of rituximab on Day 1 and bendamustine infusions on Days 1 and 2 of each 28-day cycle.

Figure 2 Study Schema



Arm A = venetoclax and rituximab (venetoclax + R); Arm B = bendamustine and rituximab (BR); 1 cycle = 28 days; CLL = chronic lymphocytic leukemia; OS = overall survival; PD = progressive disease; PO = per os; QD = once daily.

* Patients will receive venetoclax starting on Day 1 (venetoclax dose ramp-up period) as delineated in Section 4.3.2.1.1 venetoclax will then be self-administered at 400 mg per day for a maximum of 2 years from Cycle 1 Day 1 or until disease progression (whichever is earlier). Combination therapy consisting of 6 cycles of rituximab and daily venetoclax dosing will start after completion of the venetoclax ramp-up period.

All patients will have baseline tumor assessment and will be assessed for response to treatment by the investigator using standard clinical and laboratory examinations and computed tomography (CT) scans according to iwCLL guidelines (Hallek et al. 2008) at the following timepoints (selected to mirror those used in current Phase III CLL protocols [CLL10, CLL11]):

- Clinical response assessment only on Day 1 of every cycle of combination therapy
- Full response assessment, including CT scans, at interim response assessment (within 14 days of Cycle 4 Day 1)
- Clinical response assessment only at completion of combination therapy (4 weeks ± 7 days after Day 1 of the last cycle of rituximab + venetoclax [Arm A] or BR [Arm B] or Day 1 of the last treatment cycle in case of early termination)
- Full response assessment, including CT scans, at 8–12 weeks after combination therapy (defined as 8–12 weeks after Day 1 of Cycle 6 or 8–12 weeks after Day 1 of the last cycle for early termination)

Following 6 cycles of combination therapy, patients in both arms will be followed clinically every 3 months through Year 3 from initiation of combination therapy (Cycle 1 Day 1). Patients will then be followed every 6 months for an additional 2 years, study withdrawal, or end of study, whichever comes first. At each follow-up visit, patients will be assessed for response/progression by clinical assessment only. In addition, at any time during the study when clinical or laboratory findings suggest that the response may have improved from stable disease (SD) to PR or from PR to CR, imaging should be performed to confirm the response. Sites are allowed to do imaging any time during the treatment period to confirm a CR. Imaging is not routinely required to determine PD

because objective evidence of PD is most often documented by measurement of elevated peripheral CLL cells. However, when PD cannot be documented by increasing peripheral blood lymphocyte count, imaging is required to document PD detected by physical examination or suspected on the basis of symptoms. A bone marrow biopsy may also be conducted at any time during the study to confirm a CR.

A bone marrow aspirate should be obtained for MRD assessment in the bone marrow in all responders (CR+PR) at the End of Combination Treatment Response Visit. In addition, MRD samples in peripheral blood are collected at baseline, within 14 days of C4D1 (interim assessment), completion of combination therapy/early treatment termination visit (if applicable), End of Combination Treatment Response Visit, and at the timepoints specified in Appendix 1 during the follow-up or at any visit during follow-up where a patient has a response (PR or CR status). Samples will be measured at a central laboratory.

After 5 years in the study or after disease progression during the follow-up period (whichever comes first), patients will be followed annually for OS, PD (if not progressed already), and new anti-CLL therapy until end of study. Annual follow-up may be conducted by telephone contact.

Patients who receive a new anti-CLL therapy any time during follow-up in the absence of PD will be followed on the same schedule of assessment (see Appendix 1) for PD and then for OS.

Patients who discontinue all components of study therapy either prior to completion of planned therapy or prior to disease progression (e.g., for toxicity) will continue to be followed for MRD levels, PD, and OS (regardless of whether they subsequently receive new anti-CLL therapy).

An independent review of the responses of all patients will also be conducted to confirm the primary PFS endpoint, including blinded review of clinical and laboratory findings as well as blinded radiology review of imaging assessments (see Section 3.1.2).

Safety will be evaluated by monitoring the nature/frequency/severity of serious adverse events and non-serious adverse events, premature study withdrawals, deaths, effects on laboratory parameters, vital signs, physical examination, venetoclax dose delays, or effects on other safety biomarkers. Adverse events will be graded using NCI CTCAE, v4.0 (see Section 5.3.3). Laboratory safety assessments will include regular monitoring of hematology, blood chemistry, and tests of immunologic parameters.

QOL will be assessed using the MDASI, EORTC QLQ-C30, and CLL-16 module scoring manuals (see Appendix 3, Appendix 4, and Appendix 5).

A schedule of assessments is provided in Appendix 1.

3.1.1 Independent Review Committee

An IRC composed of board-certified radiologists and board-certified oncologists with experience in CLL will assess in a blinded manner all patients for response and progression on the basis of imaging results, bone marrow biopsy results, and relevant clinical data, guided by a charter specific to the independent review.

3.1.2 Independent Data Monitoring Committee

This trial includes an iDMC for review of safety and efficacy data collected during the study. Reviews by the iDMC will be conducted according to a charter written and approved prior to study initiation. Members of the iDMC will be external to the Sponsors and the study team and will follow a charter that outlines their roles and responsibilities. An independent Data Coordinating Center (iDCC) that is independent of the Sponsors will prepare analyses for review.

At the beginning of the study, intensive monitoring and analysis of all clinically significant safety events will be performed. The iDMC will assemble to review a safety analysis of significant safety events approximately 1 month after the first patient is enrolled depending on the rate of initial patient enrollment, then approximately every 2 months until 40 patients have completed 2 cycles of treatment (with approximately 20 patients in each arm). Thereafter, the iDMC will meet approximately every 6 months and subsequently at a frequency determined by the iDMC and the Sponsors according to the emerging safety profile. In addition, either the Sponsors or the iDMC can request ad hoc iDMC meetings at any time that potential safety concerns arise. The iDMC will evaluate efficacy and safety at one formal interim analysis.

3.2 END OF STUDY

The end of the study will be approximately 3 years after the last patient is enrolled, allowing for completion of the maximum duration of planned therapy (in the absence of disease progression) as well as at least 1 year of follow-up for all patients.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Combination Therapy (Experimental Group)

Rituximab has been shown to be an effective treatment for low-grade, CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy (Maloney et al. 2002; Cheson 2006).

Although the exact mechanism of action of rituximab remains unclear, it is known to induce cell death through several pathways, including CDC, ADCC, and apoptosis (Maloney et al. 2002). In vitro, rituximab-resistant lymphoma clones have been shown to up-regulate pro-survival Bcl-2 family members relative to wild-type cells and to exhibit a higher degree of resistance to numerous chemotherapeutic agents. Cutaneous B–cell lymphoma samples obtained after clinical relapse from rituximab treatment also exhibited a strong up-regulation of Bcl-2 compared with those before therapy, potentially

linking anti-apoptotic Bcl-2 proteins to therapy resistance (Wobser at al. 2007). These data suggest that by lowering the apoptotic threshold, a Bcl-2 antagonist may act synergistically with rituximab in a variety of settings.

In a xenograft model of NHL (DoHH-2), venetoclax dosed as monotherapy caused significant tumor growth delay compared with the vehicle. Combining rituximab and bendamustine with venetoclax resulted in significantly improved tumor inhibition compared with rituximab and bendamustine alone (Souers et al. 2013). Therefore, this combination may hold promise in the treatment of CD20-positive lymphoid malignancies.

3.3.1.1 Rationale for Venetoclax Dosage

Venetoclax dosing for this study was based on the experience from the single-agent Phase I dose-escalation Study M12-175 examining single-agent venetoclax in relapsed and refractory CLL patients. That study established a ramp-up schedule over several weeks in order to safely administer venetoclax, reducing the risk for TLS by more gradually reducing the leukemia cell burden prior to administration of the full target dose. The starting dose of venetoclax is 20 mg. In M12-175, the absence of laboratory evidence of TLS, the 20-mg dose is followed by 50 mg venetoclax QD for 1 week, followed by weekly increases in dose levels to a maximum dose of 600 mg. However, the dose to be used in combination with rituximab and other agents has been determined to be 400 mg for CLL. Preliminary data from Study M12-175 show that the 400 mg venetoclax dose as a single agent results in exposure that causes $>80\%$ reduction in lymphocyte counts, tumor size, and bone marrow infiltrates in most patients. These results were considered in selecting the dose for this study.

Based on recent analysis of 58 patients enrolled in different venetoclax trials and as part of modifications to the tumor lysis syndrome prophylaxis measures, starting dosing with 20 mg every day for 1 week for all patients is chosen (see Section 1.2.2.3.2).

3.3.1.2 Rationale for Rituximab Dosage

The approved body surface area (BSA)–adjusted dosing regimen of rituximab in combination with chemotherapy for front-line or relapsed CLL will be used in this study: 375 mg/m^2 at Cycle 1 followed by 500 mg/m^2 at Cycles 2–6 at intervals of 4 weeks. Evaluation of a potential PK interaction from the combination of venetoclax and rituximab is incorporated into the PK assessment plan in an ongoing study (M13-365).

3.3.1.3 Rationale for Duration of Therapy

The number of cycles of dosing (6×28-day cycles) is designed to provide a duration of treatment consistent with other therapies for CLL that have been shown to be sufficient to provide durable responses. Patients randomized to Arm A (venetoclax$+$R) who have not had disease progression after 6 cycles of therapy will continue on daily venetoclax monotherapy until disease progression or for a maximum of 2 years from Cycle 1 Day 1. In the single-agent Phase I dose-escalation Study M12-175, responses to single-agent venetoclax have been seen to improve over time as treatment continues without a fixed stopping point; thus, early termination of venetoclax treatment may prevent patients from reaching their maximal response. Treatment to progression is being evaluated in the

Phase I studies of venetoclax; so far, no evidence of unexpected late toxicities has emerged from continued treatment with venetoclax beyond 6 months.

3.3.2 Rationale for Control Group

BR is considered a relevant comparator arm, because other available recommended and/or approved therapies in this setting are either associated with high toxicity (e.g., FCR, allogeneic stem cell transplantation [ASCT], high-dose steroid combinations, and alemtuzumab) or have limited effectiveness (e.g., ofatumumab, rituximab monotherapy, or chlorambucil) (Eichhorst et al. 2011). Furthermore, BR is recommended as a second-line therapy for fit or elderly patients experiencing short durations of initial treatment response. In a Phase II trial examining the efficacy of BR in relapsed/refractory CLL, median OS was 34 months and median PFS was 15 months (Fischer et al. 2011). Alemtuzumab is recommended for treatment of patients with the 17p deletion per the NCCN Practice Guidelines in Oncology (v3.2012); however, it has been withdrawn from commercial availability in the United States and the European Union and will be available only under a compassionate use program for appropriate patients. Moreover, alemtuzumab is less effective for eradication of bulky disease (Fiegl et al. 2006; Keating et al. 2002). Although response rate to BR in relapsed CLL with the 17p deletion is low, more effective alternatives are not universally available.

3.3.2.1 Rationale for BR Dosage

Two Phase II single-arm studies have investigated BR in the previously untreated and in the relapsed/refractory CLL settings. In the previously untreated CLL study, bendamustine was dosed for 6 cycles at 90 mg/m^2 on Days 1 and 2 in combination with rituximab administered at 375 mg/m^2 for the first cycle and 500 mg/m^2 for Cycles 2–6 (Fischer et al. 2009). Preliminary results indicate an OR rate of 91%, with 33% CR rate.

In the relapsed/refractory CLL study, bendamustine was dosed for 6 cycles at 70 mg/m^2 on Days 1 and 2 when combined with rituximab administered at 375 mg/m^2 for the first cycle and 500 mg/m^2 for Cycles 2–6 (Fischer et al. 2011). In that study with 78 patients, the most common Grade 3/4 adverse events observed included neutropenia (23%), thrombocytopenia (28%), and anemia (17%). Grade 3 infections occurred in 13% of patients; dose reductions were required in 37% of patients, and 23% and 44% of patients did not receive at least 3 or all 6 cycles of treatment, respectively, most often because of toxicity. Even with this safety profile, which is not unusual with chemoimmunotherapy regimens in this patient population, BR was demonstrated to have meaningful clinical activity with an OR rate of 59% and PFS of 15 months.

In the Phase II study in relapsed/refractory CLL, rituximab was dosed at 375 mg/m^2 for the first cycle and at 500 mg/m^2 during Cycles 2–6 (Fischer et al. 2011). Because this schedule resulted in meaningful clinical activity, the same schedule will be used in the BR arm for this study.

BR chemoimmunotherapy has been shown to be associated with toxicity (e.g., myelosuppression) that can necessitate dose delays, dose reductions, and early discontinuation in patients with NHL and CLL (Fischer et al. 2011). Consensus recommendations for bendamustine dose are 70 mg/m^2 in relapsed/refractory patients either as a single agent or in combination with rituximab (Cheson et al. 2010). Patients participating in this study will be treated according to this recommendation and will therefore receive 70 mg/m^2 bendamustine on Days 1 and 2 of the cycle for 6 cycles.

3.3.3 Rationale for Patient Population

Survival in CLL patients is highly variable, ranging from less than 2 years to 20 years or more (Binet et al. 1981). Intermediate-risk (Rai Stages I and II) patients, who account for 61% of all CLL patients, have a median survival of 7–9 years. High-risk (Rai Stages III and IV) patients, who account for 8% of all CLL patients, have a median survival of 5 years.

Treatment is usually initiated when the patient becomes symptomatic or progresses to late-stage CLL. First-line treatment of CLL has evolved from single-agent therapy to combination chemoimmunotherapy (Keating et al. 1993; Johnson et al. 1996; Rai et al. 2000; Leporrier et al. 2001; Eichhorst et al. 2006; Catovsky et al. 2007; Flinn et al. 2007; Hillmen et al. 2007; Hallek et al. 2010). The choice of front-line therapy is guided by patient age, comorbidity, and Performance Status. The lack of a standard regimen for front-line patients results in a heterogeneous population of second-line patients that has been documented in other studies in the relapsed/refractory setting (Fischer et al. 2011).

For relapsed patients, single- and multi-agent therapies are options, but relapsed disease is associated with a median survival between 15 and 44 months and is highly dependent on CLL risk status and choice of regimen (Lamanna et al. 2006; Wierda et al. 2010; Fischer et al. 2011). Furthermore, the NCCN and ESMO guidelines list several options for treatment of relapsed patients (see Appendix 8), which take into account the duration of initial response because response duration has been shown to be prognostic of long-term outcome (Tam et al. 2008). ASCT is the only potentially curative treatment option for CLL patients; however, transplantation is appropriate only for a small number of younger patients and is associated with high morbidity and mortality.

In this study, eligible patients must have been treated with at least one but no more than three previous lines of therapy (a line of therapy is defined as completing 2 cycles of treatment for a given line of therapy) including at least one prior standard chemotherapy-containing regimen according to current guidelines. Multiple standard and experimental treatments are available for CLL and vary by geographic region. Therefore, relapsed/refractory CLL patients represent a heterogeneous group especially as the number of prior therapies increases. In the present study, the number of previous therapies is limited to three in order to limit this heterogeneity.

Data from clinical trials of fit individuals treated with FCR chemotherapy in the front-line setting have demonstrated long-term durable responses (Tam et al. 2008; Hallek et al. 2010). As previously noted, similar responses for relapsed/refractory patients have not been observed. Therefore, novel approaches are needed to improve the outcome of this subset of CLL patients.

In almost all cases, CLL remains an incurable disease. Moreover, treatment options are limited in the largely elderly patient population. A chemotherapy-free regimen (e.g., venetoclax+R) may have fewer side effects and represent a novel strategy for improving response rates and the morbidity and mortality of patients with relapsed/refractory CLL.

3.3.4 Rationale for Including Patients with 17p Deletion

CLL patients with the 17p deletion (resulting in loss of the p53 tumor suppressor allele) have a poor prognosis characterized by suboptimal responses to first-line and subsequent therapies. Defects in p53 are found in approximately 10%–15% of CLL patients requiring front-line therapy (Pettitt et al. 2012). Among patients with chemotherapy-refractory CLL, the frequency increases to almost 50% (Zenz et al. 2009).

There are currently no treatments approved specifically to meet the need of the 17p deletion population. For relapsed/refractory 17p deletion patients ineligible for allogeneic transplant or clinical trial, outcomes following standard therapy are significantly worse than for patients without abnormalities at 17p (Pettitt et al. 2012).

Among patients with relapsed CLL treated with FCR, those with the 17p deletion showed poorer outcomes than the overall study population. PFS and OS were 5 months and 10 months, respectively, in patients with 17p deletion, compared with 21 months and 47 months in the entire cohort. The corresponding response rates were also lower in patients with the 17p deletion (Badoux et al. 2011).

Pettitt et al. (2012) recently described the outcome of patients with the 17p deletion treated in the front-line setting or at relapse with alemtuzumab. Among the 22 relapsed patients, an OR rate of 77% was observed with a median PFS of 6.5 months (Pettitt et al. 2012). However, alemtuzumab and other approved therapies are associated with significant toxicity, limiting their use in older populations.

The mechanism of action of venetoclax is independent of the TP53 pathway. Early results from the ongoing single-agent Phase I dose-escalation Study M12-175 have demonstrated activity in 14 of 16 relapsed/refractory CLL patients with the 17p deletion. These encouraging preliminary data indicate that venetoclax may be beneficial in this unique high-risk patient population and may also represent a less toxic option when venetoclax is used in combination with rituximab.

3.3.5 Rationale for Biomarker Assessments

Venetoclax inhibits the ability of cancer cells to evade cell death, or apoptosis, by blocking the activity of the anti-apoptotic protein Bcl-2 (Korsmeyer 1999; Cory and Adams 2002; Borner 2003; Cory et al. 2003). Nonclinical studies have demonstrated a pattern of response to venetoclax based on the levels of Bcl-2 family proteins. High levels of Bcl-2 and low levels of Mcl-1 are generally predictive of response to this drug in vitro (unpublished data, Genentech, Inc.). In addition, high levels of at least one pro-apoptotic "sensor" such as Noxa or Bim are required. Furthermore, nonclinical studies have suggested that acquired rituximab resistance may occur as a result of the up-regulation of Bcl 2 (Byrd et al. 2002). Measurement of relevant RNAs, miRNAs, tumor-associated DNA alterations (such as p53 and Notch1 mutations), and proteins (including those in the Bcl-2 family) in CLL cells will be examined pretreatment, during treatment, and at the time of progression for putative stratification markers and correlation with efficacy. In addition, blood samples will be collected to determine in vitro sensitivity of CLL cells to venetoclax (EC_{50}) to evaluate whether response to venetoclax can be predicted in vitro. These studies will help to identify responsive patient populations and to develop better therapies for patients with CLL. Because these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

3.3.6 Rationale for Patient-Reported Outcome Assessments

Patients with CLL experience a high symptom burden from the underlying disease process that is compounded by the side effects of currently available therapies. These symptoms and treatment-related side effects can impact function and, subsequently, HRQoL. If the expected clinical benefit of venetoclax+R is observed in the trial, there is reason to believe that patients might observe an accompanying improvement in distinct key symptoms of the disease (i.e., reduction in fatigue, reduction in nodular pain, and decrease in night sweats). PROs will be used to capture the patients' report of these symptom changes and detect change in disease symptoms. Specifically, with PFS being a primary clinical endpoint, understanding the time to disease progression through PROs and what patients gain from disease symptoms during this time can be used to support PFS.

To comprehensively characterize treatment-related side effects between the two study arms, PROs will be used to evaluate common treatment-related side effects. It is hoped that the novel treatment approach of venetoclax+R will have a reduced side-effect profile and improved tolerability compared with traditional chemotherapy and result in an improvement in HRQoL and functioning for patients with CLL while undergoing treatment. The reduction in both disease symptoms and treatment-related side effects combined with a subsequent improvement in HRQoL might serve to reduce health economic impact for these patients.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse, determined using standard iwCLL guidelines (Hallek et al. 2008), or death from any cause, whichever comes first.

While the primary efficacy endpoint is investigator-assessed PFS, PFS based on IRC assessments will also be analyzed to support the primary analysis. [redacted]

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- IRC-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory
- Investigator-assessed PFS in the subset of CLL patients with 17p deletion identified by FISH testing at a central laboratory
- Best OR (defined as CR, CRi, nPR, and PR)rate as assessed by the investigator
- OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit, as assessed by the investigator. Disease response will be assessed according to the iwCLL guidelines (Hallek et al. 2008).
- OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit, as assessed by the IRC
- OS, defined as the time from randomization to death from any cause
- EFS, defined as the time between randomization and the date of disease progression/relapse, death from any cause, or start of a new anti-CLL therapy
- DOR, defined for patients with a best OR of CR, CRi, nPR, or PR as the time from first occurrence of a CR, CRi, nPR, or PR to disease progression/relapse, as assessed by the investigator, or death from any cause
- TTNT, defined as the time from randomization to start of new non-protocol anti-CLL therapy or death from any cause
- MRD response rate (determined as the proportion of patients with MRD negativity) at End of Combination Treatment Response Visit as measured at a central laboratory on peripheral blood and/or bone marrow samples

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events and serious adverse events
- Changes in clinical laboratory results (including hematology and chemistry) during and following administration of study treatment

- Incidence of adverse events of special interest:

  Grade ≥3 TLS and IRRs

- Measures of immune function, including serial immunoglobulin levels (IgG, IgM, IgA) following treatment with venetoclax + R or BR

3.4.3 Pharmacodynamic Outcome Measure

The pharmacodynamic outcome measure for this study is as follows:

- Serial assessment of B- and T-cell lymphocyte subsets by flow cytometry

3.4.4 Pharmacokinetic Outcome Measures

The PK outcome measures for this study include:

- Plasma venetoclax concentrations at the specified timepoints
- Apparent clearance, apparent volume of distribution, and other appropriate PK parameters of venetoclax characterized using population PK techniques, as data allow

3.4.5 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- MDASI
- EORTC QLQ-C30 and QLQ-CLL16

3.4.6 Health Economic Outcome Measure

The health economic outcome measure for this study is as follows:

- The EQ-5D questionnaire

3.4.7 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Evaluation of the relationship between response and PFS and various potential biomarkers, including Bcl-2 expression, for patients treated with venetoclax + R or BR
- Assessment of potential biomarkers that are prognostic and/or predictive of response and resistance to treatment with venetoclax + R or BR
- MRD response rate as measured at a central laboratory on peripheral blood samples and/or bone marrow aspirate samples at the disease response assessment timepoints

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this study is adult patients with relapsed or refractory CLL requiring treatment.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent
- Age ≥18 years
- Diagnosis of CLL that meets published diagnostic criteria (Hallek et al. 2008). Patients must have peripheral blood B–lymphocyte counts that clonally express CD5, CD19/20, and CD23 and are either kappa or lambda light-chain-restricted. Pro-lymphocytes may comprise no more than 55% of total circulating lymphocytes. At initial diagnosis of CLL (i.e., prior to front-line treatment), the peripheral lymphocyte count must have been >5000/mm^3. Patients must meet the following criteria for relapsed or refractory CLL (per the iwCLL guidelines [Hallek et al. 2008]):

    Relapsed disease: a patient who previously achieved a CR or PR but after a period of 6 months or more demonstrates evidence of progression

    Refractory disease: treatment failure or disease progression within 6 months after the last anti-leukemia therapy

- Previously treated with at least one but not more than three lines of therapy (a line of therapy is defined as completing at least two cycles of treatment for a given line of therapy), including at least one prior standard chemotherapy-containing regimen according to current guidelines (see Appendix 8)
- For patients with the 17p deletion, previously treated with at least one but not more than three lines of therapy, including at least one prior standard chemotherapy-containing regimen OR at least one prior alemtuzumab-containing therapy (see Appendix 8)
- Patients previously treated with bendamustine only if their DOR was ≥24 months
- Patient requires treatment in the opinion of the investigator
- ECOG performance score of ≤1 (see Appendix 7)
- Adequate bone marrow function independent of growth factor or transfusion support, within 2 weeks of screening, at screening as follows unless cytopenia is clearly due to marrow involvement of CLL:

    Platelet count ≥75,000/mm^3; in cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator), platelet count should be ≥ 30,000/mm^3

    Absolute neutrophil count (ANC) ≥ 1000/mm^3 unless neutropenia is clearly due to marrow involvement of CLL (per the discretion of the investigator)

    Total hemoglobin ≥9 g/dL unless anemia is due to marrow involvement of CLL (per the discretion of the investigator)

- Adequate renal and hepatic function, per laboratory reference range at screening, as follows:

  Calculated creatinine clearance $\geq$50 mL/min using 24-hour creatinine clearance or modified Cockcroft-Gault equation (using ideal body mass [IBM] instead of mass):

  $$\text{eCCr} = \frac{(140-\text{Age}) \bullet \text{IBM (kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

  Or, if serum creatinine is in μmol/L:

  $$\text{eCCr} = \frac{(140-\text{Age}) \bullet \text{IBM (kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/L})}$$

  (IBM) should be used:
  IBM (kg) $=$ ([height in cm $-$154] $\times$ 0.9)] $+$ (50 if male, 45.5 if female)

  AST and ALT $\leq$ 3.0 times the upper limit of normal (ULN) of the institution's normal range;

  Bilirubin $\leq$ 1.5 $\times$ ULN. Patients with Gilbert's syndrome may have a bilirubin level $>$ 1.5 $\times$ ULN, per discussion between the investigator and the Medical Monitor;

  Prothrombin time (or international normalized ratio) and partial thromboplastin time not to exceed 1.2 times the institution’s normal range (patients with an elevated prothrombin time and known lupus anticoagulant may be eligible for participation after consulting the Medical Monitor.)

- Female patients must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:

  At screening, on a serum sample obtained within 14 days prior to initiation of study treatment, and

  Prior to dosing, on a urine sample obtained on the first day of study treatment if it has been $>$7 days since obtaining the serum pregnancy test result

- Female patients who are not surgically sterile or postmenopausal (for at least 1 year) must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 30 days after study treatment or 12 months after completing therapy with rituximab, whichever is later:

  Total abstinence from sexual intercourse

  A vasectomized partner

  Hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) that started at least 3 months prior to study drug administration

  Double-barrier method (condom $+$ diaphragm or cervical cup with spermicidal contraceptive sponge, jellies, or cream)

- Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 3 months after study treatment or 12 months after completing therapy with rituximab, whichever is later:

    A partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration

    Total abstinence from sexual intercourse

    Double-barrier method (condom + diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream)

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Transformation of CLL to aggressive NHL (e.g., Richter's transformation, prolymphocytic leukemia, or DLBCL) or CNS involvement by CLL
- Underwent an allogeneic stem cell transplant
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- History of intolerance to prior bendamustine treatment (defined as toxicity requiring permanent discontinuation of bendamustine) or other contraindication to bendamustine treatment
- History of severe (i.e., requiring permanent discontinuation of prior rituximab therapy) prior allergic or anaphylactic reactions to rituximab
- Known HIV positivity
- Positive test results for chronic hepatitis B infection (defined as positive HBsAg serology)

    Patients with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly PCR HBV DNA testing.

- Positive test results for hepatitis C (HCV antibody serology testing)

    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Requires the use of warfarin (due to potential drug–drug interactions that may potentially increase the exposure of warfarin). Patients may be eligible if able to be taken off warfarin and started on an alternative anticoagulant.
- Received an anti-CLL monoclonal antibody within 8 weeks prior to the first dose of study treatment

- Received any of the following agents within 28 days prior to the first dose of study treatment:

  Any anti-cancer therapy including chemotherapy or radiotherapy and steroid therapy for anti-neoplastic intent, investigational therapy, including targeted small-molecule agents

- Has not recovered to less than Grade 2 clinically significant adverse effect(s)/toxicity(ies) of any previous therapy
- Received potent CYP3A4 inhibitors (such as fluconazole, ketoconazole, and clarithromycin) within 7 days prior to the first dose of study treatment (see Appendix 9)
- Received potent CYP3A4 inducers (such as rifampin, carbamazepine, phenytoin, St. John's wort) within 7 days prior to the first dose of study treatment (see Appendix 9)
- History of prior venetoclax treatment
- Consumed grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of study treatment
- A cardiovascular disability status of New York Heart Association Class ≥3. Class 3 is defined as cardiac disease in which patients are comfortable at rest but have marked limitation of physical activity due to fatigue, palpitations, dyspnea, or anginal pain.
- A significant history of renal, neurologic, psychiatric, endocrine, metabolic, immunologic, cardiovascular, or hepatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes.
- Major surgery within 30 days prior to the first dose of study treatment
- A patient who is pregnant or breastfeeding
- History of prior other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

  Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study

  Other cancers not specified above that have been curatively treated by surgery and/or radiation therapy from which patient is disease-free for ≥5 years without further treatment.

- Malabsorption syndrome or other condition that precludes enteral route of administration
- Known allergy to both xanthine oxidase inhibitors and rasburicase
- Evidence of other clinically significant uncontrolled condition(s) including but not limited to uncontrolled systemic infection (viral, bacterial, or fungal)
- Vaccination with a live vaccine within 28 days prior to randomization

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

Randomization will be performed by an interactive voice/Web-based system (IxRS). Patients will be assigned in 1:1 ratio to one of the two treatment arms through a block stratified randomization procedure. The randomization scheme will ensure approximately equal sample sizes in the two treatment groups in regard to the following stratification factors:

- 17p deletion by local testing (yes/no)
- Risk status: high risk or low risk

  High risk: defined as harboring 17p deletion or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy

  Low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemoimmunotherapy
- Geographic region (United States/Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America)

A unique patient number will be assigned at randomization. This patient number will be used to identify the patient in the electronic data capture (EDC) system and all other data sources.

The iDCC and iDMC will be unblinded. Assessments by the IRC will be blinded.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

The Sponsors will be supplying all study treatments for this study (venetoclax, rituximab, and bendamustine).

4.3.1.1 Venetoclax

Venetoclax (GDC-0199 [ABT-199]) is manufactured by AbbVie, Inc. and will be supplied as oral tablets of 10 mg, 50 mg, and 100 mg strength. Venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled (either single-panel or booklet) per individual country requirements. Label must remain affixed to the supplies. Venetoclax drug must be stored at 15°C–25°C (59°F–77°F). The investigational product is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for patient use or returned to the Sponsors.

For further details, see the Venetoclax Investigator's Brochure.

4.3.1.2 Rituximab

Rituximab is manufactured by Genentech, Inc., as the licensed product Rituxan® in the United States and Canada. For the rest of the world, rituximab is manufactured by F. Hoffmann–La Roche Ltd. (Roche) as the licensed product MabThera®. It is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in 100-mg (10-mL) and 500-mg (50-mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with sterile water for Injection. The pH is adjusted to 6.5. Vials are for single use. Each vial and carton will be labeled (either single-panel or booklet) per individual country requirements. Label must remain affixed to the supplies.

Rituximab vials must be stored at 2°C–8°C (36°F–46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours and has been shown to be stable for an additional 12 hours at room temperature. However, since rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

For further details, see the local prescribing information for Rituxan®/MabThera®.

4.3.1.3 Bendamustine

Bendamustine HCl is marketed by Cephalon as the licensed product Treanda® for the United States and is marketed in Germany by Mundipharma International Corporation Ltd, under the name Levact®. Bendamustine will be supplied in individual cartons containing single-use vials of 100 mg bendamustine HCl as lyophilized powder. Each vial and carton will be labeled (either single-panel or booklet) per individual country requirements. The label must remain affixed to the supplies. First, dissolve contents of the bendamustine vial containing 100 mg of bendamustine hydrochloride in 40 mL of Water for Injection, while shaking. Once a clear solution has been obtained (generally after 5–10 minutes), the total bendamustine dose is diluted immediately to a final volume of 500 mL. Bendamustine is formulated for IV administration in either 0.9% sodium chloride injection or 2.5% dextrose/0.45% sodium chloride. Each vial and carton will be labeled (either single-panel or booklet) per individual country requirements. Label must remain affixed to the supplies.

Bendamustine should be stored at 15°C–25°C (59°F–77°F). It is to be retained in the original carton until time of use to protect from light. Bendamustine should be prepared for administration as close as possible to the time of administration. Once diluted with sodium chloride or dextrose/sodium chloride, the final admixture is stable for 24 hours if Treanda® is used and for 2 days if Levact® is used and when stored refrigerated (2°C–8°C or 36°F–47°F) or for 3 hours when stored at room temperature (15°C–30°C or

59°F–86°F) and room light. Administration of bendamustine must be completed within this period.

For further details, see the local prescribing information for Treanda®/Levact®.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Venetoclax

Following an initial venetoclax ramp-up period (see Section 4.3.2.1.1), patients randomized to Arm A (venetoclax + R) will take venetoclax 400 mg daily orally in combination with rituximab administered intravenously on Day 1 of each 28-day cycle for 6 cycles. After completion of combination therapy, patients will continue to take venetoclax 400 mg daily orally as monotherapy until disease progression or for a maximum of 2 years from Cycle 1 Day 1.

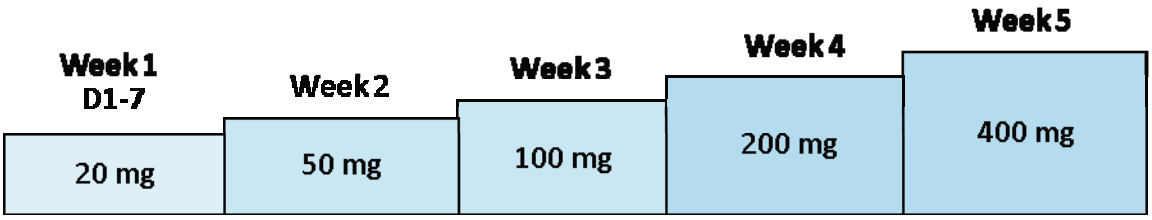
4.3.2.1.1 Venetoclax Ramp-Up Period

To mitigate potential serious complications of TLS, patients will require close clinical and laboratory monitoring during the venetoclax ramp-up period. See Section 4.4.1.2 for details of the TLS prophylaxis and monitoring guidelines.

All patients randomized to Arm A will start the study by receiving 20 mg of venetoclax daily for at least 7 days. Patients who demonstrate evidence of electrolyte abnormalities suggestive of TLS during the 24 hours following the initial 20-mg dose will receive appropriate treatment to resolution prior to receiving their next daily dose of venetoclax (see Appendix 11 for Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome).

Venetoclax dose increases will then occur weekly, starting with 50 mg/day for 1 week followed by 100 mg/day for 1 week, 200 mg/day for 1 week, and the final dose of 400 mg/day for 1 week. All patients should receive any intended dose for at least 7 days before increasing to the next higher dose. The duration of the venetoclax ramp-up period will be 5 weeks as shown in Figure 3. Patients will then continue taking venetoclax 400 mg daily as directed by the investigator.

Figure 3 Venetoclax Dosing Scheme during the Ramp-Up Period



D = day.

4.3.2.1.2 Venetoclax in Combination with Rituximab

After the patient has completed the venetoclax ramp-up period and received the target dose of 400 mg of venetoclax for a total of 7 days with no evidence of electrolyte abnormalities suggestive of LTLS or any electrolyte abnormalities resolved per protocol Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (see Appendix 11), the patient will begin combination therapy consisting of 6 cycles of rituximab (infusions occurring on Day 1 of each 28-day cycle; see Section 4.3.2.2) in combination with the daily dose of venetoclax. All patients must receive prophylaxis for TLS (see Section 4.4.1.2) prior to the initiation of venetoclax and rituximab treatment. On days when venetoclax and rituximab are given, venetoclax will be taken at least 30 minutes prior to starting the rituximab infusion.

Patients will self-administer venetoclax tablets by mouth QD. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of a low-fat breakfast. Examples of a low-fat breakfast include 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jam and 8 ounces/240 mL of skim milk (319 calories and 8.2 g fat) or 1 cup/30 g of cereal, 8 ounces/240 mL of skim milk, 1 slice of toast with jam, 1 cup/240 mL of apple juice, and 1 cup/240 mL of coffee or tea (520 calories and 2 g fat). If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be provided. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken with food within 8 hours after the missed dose. Otherwise, the dose should not be taken.

Patient compliance in taking the assigned daily dose of venetoclax will be assessed by standard pill counts. Bottles containing venetoclax tablets will be given to patients at regular scheduled visits. Previously distributed bottles will be returned to the clinic and tablets counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Any overdose or incorrect administration of venetoclax should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Guidelines for venetoclax dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

4.3.2.2 Rituximab

Rituximab will be administered to patients in both treatment arms at 375 mg/m^2 IV on Day 1 of Cycle 1 followed by 500 mg/m^2 on Day 1 of Cycles 2 through 6 (total of six infusions of rituximab).

For patients in Arm A (venetoclax + R): on days when venetoclax and rituximab are given, venetoclax will be taken at least 30 minutes prior to starting the rituximab infusion.

For patients in Arm B (BR): on days when rituximab and bendamustine are to be administered, rituximab can be administered before or after bendamustine. There should be 30 minutes between administering the two agents.

The patient's BSA calculated at screening should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by $>10\%$ from screening. In obese patients, there is no cap on BSA, and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥ 30 as measured in kilograms divided meters squared).

During the treatment period, rituximab must be administered to patients in a clinical (inpatient or outpatient) setting. Rituxan should be administered only by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (such as the Braun Infusomat Space) should be used to control the infusion rate of rituximab. Administration sets with polyvinyl chloride, polyurethane, or polyethylene as a product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption. See Table 1 for instructions regarding first and subsequent infusions of rituximab.

After the end of each dose of rituximab, patients should be observed for 1 hour. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

Rituximab should not be administered as an IV push or bolus. IRRs may occur.

Premedication consisting of acetaminophen, diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion. Premedication may attenuate IRRs. Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

Table 1 Administration of First and Subsequent Infusions of Rituximab

First Infusion (Cycle 1 Day 1)	Subsequent Infusions
Begin infusion at an initial rate of 50 mg/h. If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/h increments every 30 minutes, to a maximum of 400 mg/h. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/h and follow instructions for the first infusion. If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/h), begin the infusion at a rate of 100 mg/h. If no infusion reaction occurs, increase the infusion rate in 100-mg/h increments every 30 minutes, to a maximum of 400 mg/h. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

h = hour.
Note: A fast infusion is not allowed.

Any overdose or incorrect administration of rituximab should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Guidelines for rituximab dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

4.3.2.3 Bendamustine

Patients randomized to Arm B (BR) will receive bendamustine 70 mg/m^2 administered intravenously on 2 consecutive days of each 28-day cycle for 6 cycles, in combination with rituximab administered intravenously on Day 1 of each 28-day cycle for 6 cycles (see Section 4.3.2.2 for details of rituximab dosage and administration).

BSA will be calculated at screening and on Day 1 of Cycle 1. The BSA calculated at screening should be used to calculate the dose of bendamustine throughout the study unless the patient's weight increases or decreases by >10% from screening. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥30 kg/m^2).

Bendamustine will be administered over 30 to 60 minutes on Days 1 and 2 of each 28-day cycle for a total of 6 cycles. On days when rituximab and bendamustine are to be administered, rituximab can be administered before or after bendamustine.

Premedication with anti-emetics may be administered as per institutional guidelines (see Section 4.4.1). Granulocyte colony-stimulating factor (G-CSF) may be administered as primary prophylaxis in each cycle of therapy, per the American Society of Clinical Oncology (ASCO) guidelines or each site's institutional standards.

Any overdose or incorrect administration of bendamustine should be noted on the Bendamustine Administration eCRF. Adverse events associated with an overdose or incorrect administration of bendamustine should be recorded on the adverse event eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (venetoclax, rituximab, bendamustine) will be provided by the Sponsors. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsors with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsors. The site must obtain written authorization from the Sponsors before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Venetoclax

Currently, the Sponsors do not have any plans to provide venetoclax or other study interventions to patients after conclusion of the study (unless required by country-specific regulations) or any earlier patient withdrawal. The Sponsor will evaluate the appropriateness of continuing to provide venetoclax to study patients after evaluating the primary efficacy outcome measure and safety data gathered in the study; these analyses may be conducted prior to completion of the study. If these data are medically and statistically significant, the Sponsors may amend the protocol to continue to provide venetoclax in an open-label extension study to patients in the treatment arm who have shown a demonstrable benefit from venetoclax treatment during this study (as measured by PFS). This open-label extension study would continue until venetoclax is

commercially available to the participating patients in their countries or until the Sponsors cease producing or studying venetoclax.

4.4 CONCOMITANT THERAPY AND FOOD

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to the initiation of study treatment through the end of treatment. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use for the duration of the study or at least 30 days after the last dose of study drug or 1 year after the last dose of rituximab, whichever is longer.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin) if clinically indicated. G-CSF may be administered as primary prophylaxis in each cycle of therapy, per the ASCO guidelines (Smith et al. 2006) or each site's institutional standards.

Anti-emetic therapy may be instituted for any patient if clinically indicated. Bendamustine has a moderate risk of emesis (Cheson et al. 2010). It is recommended that bendamustine infusions be administered following premedication with a serotonin (5-HT3) antagonist (i.e., dolasteron, ondansetron, etc.) or per institutional practice.

4.4.1.1 Premedication before Rituximab

Premedication may attenuate IRRs. The following premedication is required prior to rituximab therapy:

- Acetaminophen (650–1000 mg) at least 30 minutes prior to the start of all infusions
- Diphenhydramine (25–50 mg) approximately 30 minutes prior to the start of the first infusion and mandatory for all subsequent infusions unless previous antibody infusions did not result in an IRR greater than NCI CTCAE Grade 1 and there was no interruption to the infusion. (Another suitable antihistamine is also acceptable and must follow the preceding guidelines.)

A single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered with rituximab if this is the usual practice at the site.

Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

4.4.1.2 Prophylaxis and Management of Tumor Lysis Syndrome

TLS is a risk for patients with CLL who are treated with high–cell-killing agents. Clinical data from CLL patients treated to date with venetoclax suggest that patients with baseline lymph nodes $\geq$ 5 cm diameter are at a greater risk for TLS than those with baseline lymph nodes $<$ 5 cm. In addition, the data showed that creatinine clearance of $\leq$ 80 mL/min at screening was a secondary risk factor for TLS. A detailed description of risk factors for developing tumor lysis following treatment with venetoclax is available in the Venetoclax Investigator's Brochure. The section below describes the management of patients throughout dosing (as described in Section 4.3.2) based on their risk factors for developing TLS identified upon study entry.

On the basis of the data review performed by the Sponsors, the following are three TLS risk categories identified:

1. TLS low-risk**:** the presence of all measurable lymph nodes with the largest diameter $<$5 cm by radiographic assessment AND absolute lymphocyte counts $<25\times10^9$/L.
2. TLS medium-risk: the presence of all measurable lymph nodes with the largest diameter $\geq$5 cm and $<$10 cm by radiologic assessment OR absolute lymphocyte count $\geq25\times10^9$/L.
3. TLS high-risk: the presence of any lymph node with the largest diameter $\geq$10 cm by radiologic assessment OR the presence of BOTH an absolute lymphocyte count $\geq25\times10^9$/L AND a measurable lymph node with the largest diameter $\geq$5 cm by radiologic assessment.

All patients enrolling in the study will be assessed at screening and categorized in a TLS risk category as described above.

Further details of TLS prophylaxis and monitoring are presented in the following with summary at the end of Table 2.

Initial Doses: 20 and 50 mg

All patients, irrespective of their TLS risk category, must receive the following TLS prophylaxis measures prior to the initiation of the first doses of venetoclax:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax and rituximab is completed
- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to the start of treatment and continued for at least 24 hours after the first dose
- Serum chemistry and hematology laboratory samples must be drawn anytime within 72 hours prior to first dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax. If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, first dose of venetoclax must be delayed until

resolution and management per the protocol Appendix 11, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome, must be initiated. If active correction of electrolytes was performed, the first dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

TLS Low Risk

- Low-risk patients will receive their initial doses of 20 and 50 mg as outpatients.
- For patients unable to maintain oral hydration at 1.5–2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

  For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from “before dosing” laboratory values are not required to be available prior to initiating venetoclax treatment but rather will serve only as a baseline for post-dosing laboratory results comparisons.

  The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

  Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

  Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

- Medium-risk patients who have creatinine clearance ≥80 mL/min will receive their initial doses of 20 and 50 mg as outpatients. Patients with creatinine clearance <80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator) may be handled as high-risk patients (see the High Risk section for details of hydration, laboratory, etc.).
- In addition to oral hydration stated above, IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from “before dosing” laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS High Risk

- High-risk patients will be hospitalized to receive their initial doses of 20 and 50 mg. Hospitalization will begin the evening prior to each initial dose of venetoclax and continue for 24 hours after.
- Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.
- Rasburicase must be administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or Cairo-Bishop threshold of 476 µmol/L). For patients with a contraindication to rasburicase (i.e., glucose-6-phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in Section 4.5.1.7.
- Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- Serum chemistry, hematology, and vital signs will be performed before dosing and at 4 (serum chemistry only), 8, 12 (serum chemistry only), and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour post-dose laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug. Additional laboratory assessments may be performed per investigator discretion.

Subsequent Dose Increases during the Venetoclax Ramp-Up Period: 100, 200, and 400 mg

All patients, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to subsequent dose increases of venetoclax:

- Continued administration of an oral uric acid reducer as indicated above.

- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged at subsequent dose increases for patients unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Serum chemistry and hematology laboratory samples must be drawn within 72 hours prior to dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to each dose increase of venetoclax, or the patient should receive additional prophylactic treatment prior to dosing. If clinically significant laboratory abnormalities are observed in this laboratory assessment, dose of venetoclax must be delayed until resolution, and management per the protocol Appendix 11, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome, must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing. If active correction of electrolytes was performed, the first or subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

TLS Low Risk

- Low-risk patients will receive the subsequent dose increases (100, 200, and 400 mg) as outpatients.
- Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and at 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

  For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from “before dosing” laboratory values are not required to be available prior to initiating venetoclax treatment but rather will serve only as a baseline for post-dosing laboratory results comparisons.

  The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

  Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

  Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

- Medium-risk patients who have creatinine clearance ≥ 80 mL/min will receive their subsequent dose increases as outpatient. Patients with creatinine clearance

< 80 mL/min and/or who have high tumor burden (defined per the discretion of the investigator) may be hospitalized.

- For patients who receive this subsequent dose increases as outpatient, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

  For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not required to be available prior to initiating venetoclax treatment but rather will serve only as a baseline for post-dosing laboratory results comparisons.

  The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

  Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

  Additional laboratory assessments may be performed per investigator discretion.
- For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 4 (serum chemistry only), 8, 12 (serum chemistry only), and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.
- IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate for patients who are hospitalized.

TLS High Risk

- High-risk patients with creatinine clearance of ≥ 80 mL/min will receive the subsequent dose increases as outpatients. Patients with creatinine clearance < 80 mL/min and/or high tumor burden (defined per the discretion of the investigator) may be hospitalized. Hospitalization will begin the evening prior to the dose of venetoclax and continuing for 24 hours after.
- IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.
- For patients not hospitalized, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

  For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and

were within normal limits, results from “before dosing” laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

- For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be performed before dosing and 4 (serum chemistry only), 8, 12 (serum chemistry only), and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.
- Additional laboratory assessments may be performed per investigator discretion.

Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose held until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per Appendix 11, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome. If active correction of electrolytes was performed, the first dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours. Any time during the ramp-up period, if venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). Dose must be resumed at one lower dose level if dose held more than 7 days with the exception of initial dose level of 20 mg (400 mg → 200 mg, 200 mg → 100 mg, 100 mg → 50 mg, 50 mg → 20 mg). All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose.

First Rituximab Dose

All patients will have the following procedures regardless of TLS risk category:

- The first dose of rituximab will be given in an outpatient setting. Patients may be hospitalized for the first dose of rituximab at the investigator’s discretion following discussion with the Medical Monitor.
- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged for patients unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.

Venetoclax will be taken at least 30 minutes prior to starting the rituximab infusion.

Serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing of venetoclax. Laboratory samples should be sent and analyzed immediately. Results from predose laboratory values are not required to be available prior to initiating venetoclax treatment provided laboratory values obtained within 24 hours before dosing were within normal limits. The 8-hour laboratory results must be reviewed prior to the patient leaving the clinic.

The 24-hour chemistry values must be reviewed before the patient receives the next day dose of venetoclax. If there is no evidence of TLS 24 hours after rituximab and venetoclax dose, patients can continue on venetoclax daily dosing.

Patients who develop any electrolyte changes suggestive of TLS should have his or her subsequent venetoclax dose held until the electrolyte abnormalities resolve and undergo aggressive management and further monitoring per Appendix 11, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome. If active correction of electrolytes was performed, the first dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.

Downgrading TLS Risk Category

Patients classified as TLS high-risk at screening due to an absolute lymphocyte count $\geq 25 \times 10^9$/L AND a measurable lymph node with the largest diameter $\geq$ 5 cm but less than 10 cm by radiologic assessment may have a re- evaluation of their TLS risk category based on their most recent ALC for dose increases above 50 mg. Based on those results, one of the following two options may be implemented:

- If the patient's ALC decreases to $< 25 \times 10^9$/L, the patient may be categorized as TLS medium- risk and follow the management guidelines for the TLS medium-risk category for subsequent dose increases (to 100, 200, 400 mg) of venetoclax during the Ramp-Up Period.
- If the patient's ALC remains $\geq 25 \times 10^9$/L, the patient will remain in the TLS high-risk category and continues to follow management guidelines for TLS high-risk patients for subsequent dose increases of venetoclax during the Ramp-Up Period. Re-assessment of the patient's TLS risk category can occur prior to each subsequent dose increase.

Table 2 Summary of TLS Prophylaxis and Monitoring Measures

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e]
TLS low-risk	20, 50, 100, 200, 400 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax and rituximab is completed.	No	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.
TLS medium-risk	20 and 50 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax and rituximab is completed.	No [c, d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.
	100, 200, 400 mg	Continue oral uric acid reducer as above.		Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	

Table 2 Summary of TLS Prophylaxis and Monitoring Measures (cont.)

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e]
TLS high-risk	20 and 50 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax and rituximab is completed. Rasburicase must be administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or Cairo-Bishop threshold of 476 µmol/L). For patients with a contraindication to rasburicase (i.e., glucose 6 phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in Section 4.5.1.7.	Yes [d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 4 (serum chemistry only), 8, 12 (serum chemistry only), and 24 hours after dosing timepoints. Samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug

Table 2 Summary of TLS Prophylaxis and Monitoring Measures (cont.)

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e]
	100, 200, 400 mg	Continue oral uric acid reducer as above	No [c, d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5–2L) will be given in the outpatient setting during the clinic stay.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

[a] For patients unable to maintain oral hydration at 1.5–2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended (unless being hospitalized) in order to assure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

[b] Results from pre-dose laboratory values are not required to be available prior to initiating venetoclax treatment provided laboratory values obtained within 24 hours before dosing were within normal limits. For laboratory samples drawn on days on study treatment, "before dosing" laboratory samples should be drawn within 0–4 hours before the dose. Other laboratory samples occurring on the same day should be obtained within a ± 15-minute window of any exact scheduled time. Any laboratory tests occurring at time intervals greater than or equal to 24 hours after dose should be obtained within a ± 2 hour window of the scheduled time.

[c] Patients with creatinine clearance < 80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator) may be handled as TLS high-risk patients.

[d] Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

[e] Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have subsequent venetoclax dose held until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per Appendix 11. If active correction of electrolytes is performed, the first or subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours. Any time during the ramp-up period, if venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). Dose must be resumed at one lower dose level if dose held more than 7 days with the exception of initial dose level of 20 mg (400 mg → 200 mg, 200mg → 100 mg, 100 mg → 50 mg, 50 mg→ 20 mg).

4.4.1.3 Prophylaxis for Infections

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial or Pneumocystis infections is permitted. (Although there is a potential for drug–drug interactions, there is likely to be limited potential clinical effects, therefore trimethoprim sulfamethoxazole [Bactrim®] can be considered for Pneumocystis prophylaxis with close clinical monitoring.) The Medical Monitor should also be consulted regarding any consideration of the use of azoles as anti-fungal prophylaxis or therapy, because of the potential for drug–drug interactions.

4.4.1.4 Prophylaxis of Hepatitis B Reactivation

Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the standard of care may be treated prophylactically.

4.4.2 Prohibited and Cautionary Therapy

Use of the following therapies is prohibited during the study treatment period:

- Any therapies intended for the treatment of leukemia whether U.S. Food and Drug Administration (FDA)-approved or experimental (outside of this study) including:
  - Cytotoxic chemotherapy
  - Radiotherapy
  - Immunotherapy
  - Systemic steroid therapy
- Anti-retroviral medications
- Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate)
- Systemic steroid therapy either during or within 7 days prior to the first dose of study treatment with the exception of inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease, single infusions of hydrocortisone prior to rituximab infusions, topical steroids, or replacement corticosteroid therapy for an inherited or acquired deficiency
- CYP1A2 inhibitors and inducers (because of possible interaction with bendamustine, a CYP1A2 substrate)

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or following study treatment until B cell levels have returned to normal.

Use of the following therapies is prohibited or cautionary during the study treatment period due to drug-drug interactions:

- Medications prohibited during ramp-up period and cautionary at the designated dose of venetoclax (400 mg) include the following:
  - Strong and moderate CYP3A inhibitors

Prohibited during ramp-up period (consider alternative medications). If patient requires use of these medications at the designated dose, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

Strong and moderate CYP3A inducers

Prohibited during ramp-up period (consider alternative medications). If patient requires use of these medications at the designated dose, use with caution and contact the medical monitor for guidance.

- Cautionary medications include the following:

  Warfarin

  Weak CYP3A inducers

  Weak CYP3A inhibitors

  P-gp substrates

  BCRP substrates

  OATP1B1 and OATP1B3 substrates

  P-gp inhibitors

  BCRP inhibitors

  OATP1B1 and OATP1B3 inhibitors

A sample list of prohibited medications and cautionary medications due to drug-drug interactions can be found in Appendix 9. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, please refer to the appropriate product label.

4.4.3 Prohibited Food

Use of the following foods is prohibited during the study and for at least 3 days prior to initiation of study treatment:

- Grapefruit
- Grapefruit juice
- Grapefruit-containing products
- Seville oranges (including marmalade containing Seville oranges)
- Star fruit

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, cancer history (including prior cancer therapies and procedures), smoking history, and all medications (e.g.,

prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.1.2 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History/Surgical History eCRF. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Targeted physical examinations should be limited to systems of primary relevance—that is, cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen).

Changes from baseline abnormalities at subsequent visits should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Height is to be recorded at screening only. Weight is to be recorded in the standing position (if possible); please see Appendix 1.

BSA will be calculated by the formula of Mosteller (1987) or site standard formula, as follows:

$$\text{BSA } (m^2) = \{[\text{Height (cm)} \times \text{Weight (kg)}]/3600\}^{1/2}$$

BSA calculated at screening should be used to calculate the dose of rituximab and of bendamustine throughout the study unless the patient's weight increases or decreases by $>10\%$ from screening. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥ 30 kg/m^2).

4.5.1.3 Vital Signs and ECOG Performance Status

Vital signs will include measurements of temperature, heart rate, and systolic and diastolic blood pressure after the patient has been in a seated position for 5 minutes.

ECOG Performance Status (see Appendix 7) will be recorded for patients at screening and at subsequent visits as described in the Schedule of Assessments (Appendix 1).

4.5.1.4 Electrocardiogram

Twelve-lead resting ECGs will be obtained at screening and at subsequent visits, as clinically indicated.

Digital ECG recordings must be obtained at each specified timepoint. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.1.5 Assessment of Left Ventricular Ejection Fraction

Baseline assessment of ejection fraction will be made at screening by either echocardiogram or multi-gated acquisition (MUGA) scan. Subsequent evaluations of left ventricular ejection fraction (LVEF) will be made as clinically indicated for patients who develop signs of cardiac compromise. The decision to enroll a patient with significant cardiac disease in the study will be made by the investigator and Medical Monitor.

4.5.1.6 Tumor and Response Evaluations

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator and by the IRC on the basis of physical examinations, imaging studies, laboratory results, and bone marrow examinations, using iwCLL response criteria for CLL (Hallek et al. 2008) (see Appendix 10).

All patients must have clinical response assessments (including targeted physical examination and laboratory examinations) at screening, Day 1 of every cycle during the combination therapy, at interim response assessment (within 14 days of Cycle 4 Day 1), after combination therapy (defined as 4 weeks after Day 1 of Cycle 6 or 4 weeks after Day 1 of the last cycle for early termination), and at 2–3 months after Day 1 of the last cycle of combination therapy.

All patients must have CT scans (or magnetic resonance imaging [MRI] if CT is contraindicated) of the neck (if clinically indicated), chest, abdomen, and pelvis with IV and oral contrast at screening, interim response assessment (within 14 days of Cycle 4 Day 1) and 2–3 months after completion of combination therapy (or 4 weeks after Day 1 of the last cycle for early termination). A follow-up scan must also be performed for patients who meet all clinical and laboratory criteria for an initial CR or PR at subsequent assessment timepoints. Sites can do imaging to confirm a PR or CR at any time during the study. The method of imaging should be consistent for each patient at subsequent timepoints.

Patients who have not progressed after the 6 cycles of combination therapy will then be followed with response assessments at every follow-up visit until progression or close of study, whichever occurs first. Assessments will be based on hematological status and targeted physical examination. Additional imaging evaluations should be performed to confirm a suspected change in response status, that is, SD to PR or PR to CR/CRi. If a patient's response improves to a CR or CRi during further follow-up, bone marrow examination must be performed to confirm the CR.

If at any time during the study, a patient exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen, or lymph nodes on physical examination) in the absence of laboratory or histopathologic changes meeting the criteria for PD, then additional assessments including imaging studies and/or bone marrow examination (in setting of new cytopenias) must be performed within 2 weeks to confirm or rule out PD.

Imaging evaluation for response assessment may be limited to areas of prior involvement only, if required by local regulatory authorities. Provisions will be made to collect and store all imaging studies for IRC review.

Bone marrow examinations should include aspirate and biopsy for morphology and biomarker studies, and are required at screening. For those patients who have achieved a CR or CRi (including an imaging evaluation indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR 2–3 months following the initial clinical assessment of the CR. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. Any additional/unscheduled bone marrow examinations performed during the study will be at the discretion of the investigator. Results of all bone marrow assessments should be forwarded to the Sponsors.

A bone marrow aspirate should be obtained for MRD assessment in the bone marrow in all responders (CR+PR) at the End of Combination Treatment Response Visit. In addition, MRD samples in peripheral blood will be collected at baseline, within 14 days of C4D1 (interim response assessment), completion of Combination Therapy/Early Treatment Termination Visit (if applicable), End of Combination Treatment Response Visit, and at the timepoints specified in Appendix 1 during the follow-up or at any visit during follow-up where a patient has a response (PR or CR status). Samples will be measured at a central laboratory.

4.5.1.7 Laboratory Assessments

For laboratory samples drawn on days on study treatment, "before dosing" laboratory samples should be drawn within 0–4 hours before the dose. Other laboratory samples occurring on the same day should be obtained within a ±15-minute window of any

scheduled time. Any laboratory tests occurring at time intervals greater than or equal to 24 hours after dose should be obtained within a ±2-hour window of the scheduled time.

Local Laboratory Assessments

Samples for the following standard laboratory tests will be sent to the study site's local laboratory for analysis:

- 17p deletion by FISH testing (the results will be used to determine 17p deletion status as positive or negative for study enrollment). Results from a prior positive laboratory test may be used if available or from a negative test if testing was done within 8 weeks of the screen date. In the event a local FISH test is not available, the result of the central test may be used by the site for randomization.
- Hematology: complete blood count (hemoglobin, hematocrit, RBC count, WBC), platelet count, ANC, ALC, and percent or absolute differential counts (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Quantitative immunoglobulins (IgA, IgG, IgM)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea (when BUN not available), creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid

  Please note that at room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation in samples collected after treatment with rasburicase:

  Uric acid must be analyzed in plasma.

  Blood must be collected into prechilled tubes containing heparin anticoagulant. **Immediately immerse plasma samples for uric acid measurement in an ice water bath.**

  Plasma samples must be prepared by centrifugation in a precooled centrifuge (4°C).

  Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.
- Viral serology and detection:

  Hepatitis B (HBsAg and HBcAb)

  Note: Monitoring of HBV-DNA levels through a central laboratory is mandatory for patients who are positive for HBcAb and enter the study with undetectable HBV-DNA. For instructions on the management of these patients, see Section 5.1.2.3.

  Hepatitis C virus antibody (also HCV RNA by PCR if the patient is HCV-antibody-positive)
- Serum pregnancy test (females)
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood)

- Coagulation (INR, aPTT/PTT, PT)
- Serum β2-microglobulin

Central Laboratory Assessments

Samples for flow cytometry, PK assessments, and bone marrow assessments will be sent to one or several central laboratories or to Genentech, Inc. for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- CLL prognostic factors, IgVH mutational status, serum β2-microglobulin (if local test is unavailable), p53 mutation status, and interphase FISH for chromosomal abnormalities, including central confirmation of 17p deletion, 11q deletion, 13q deletion, and trisomy 12
- Lymphocyte subset counts: whole-blood samples will be analyzed by flow cytometry for B cells (CD19+) and T-cell subsets (CD3+, CD4+, CD8+) and NK cells (CD16+, CD56+).
- MRD: MRD measurements (in peripheral blood and in bone marrow aspirate [when applicable]) will be performed at a central laboratory by an accepted methodology.
- Blood and bone marrow aspirate for Bcl-2 family expression (including Bcl-2:Bim complex) by RNA and protein
- Formalin fixed bone marrow biopsy (or other tumor biopsy) for Bcl-2 family expression by immunohistochemistry
- Peripheral blood for PK analysis, in vitro sensitivity to venetoclax and for pharmacogenomics
- HBV DNA by PCR in HBcAb positive patients at screening and then follow-up for patients who are positive for HBcAb and enter the study with undetectable HBV-DNA. For instructions on the management of these patients, see Section 5.1.2.3.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.1.8 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of venetoclax. The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires on paper (EORTC QLQ-C30, EORTC CLL-16, and EQ-5D) should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment. For the MDASI questionnaire, an interactive voice response solution (IVRx) will be used to capture PRO questionnaire data. The data will be transmitted to a centralized database at the IVRx vendor. The data can be accessed by appropriate study personnel securely via the Worldwide Web.

The MDASI (Cleeland et al. 2000) is a cancer related multi-symptom, valid, and reliable self-report questionnaire for clinical and research use. It consists of 19 items over two scales that assess symptom severity and symptom interference with different aspects of a patient's life. Thirteen items (i.e., pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, and numbness or tingling) ask patients to rate how severe the symptoms were when "at their worst" in the last 24 hours. An additional six items ask patients to rate how much the symptoms have interfered with six areas of function (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. Additionally, the MDASI contains tumor-specific modules to assess disease-specific symptoms. For this study, to specifically assess CLL symptoms and treatment side-effects, patients will rate six additional symptoms (night sweats, fevers and chills, lymph node swelling, diarrhea, bruising easy or bleeding, and constipation). The MDASI items are rated from 0 to 10, with 0 indicating that the symptom is either not present or does not interfere with the patient's activities and 10 indicating that the symptom is "as bad as you can imagine" or "interfered completely" with the patient's life. The MDASI takes approximately 5 minutes to complete. The MDASI assessment will be conducted using IVRx at the specified timepoints in Appendix 1.

The EORTC QLQ-C30 is a validated and reliable self-report measure (Fayers et al. 1999) consisting of 30 questions incorporated into five functional scales (physical, role, cognitive, emotional, and social scales), three symptom scales (fatigue, pain, nausea, and vomiting scales), and a global health status/global quality-of-life scale. The remaining single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) assess the additional symptoms experienced by patients with cancer and the perceived financial burden of treatment. The EORTC QLQ-CLL16 module is designed for patients with Stage 0 to Stage 4 CLL. It is composed of 16 questions that address five domains of HRQoL important in CLL. There are three multi-item scales on fatigue (two items), treatment side-effects and disease symptoms (eight items), and infection (four items), and two single-item scales on social activities and future health worries. The EORTC QLQ-CLL16 module is specific to CLL and is administered in addition to the core questionnaire (EORTC QLQ-C30). The EORTC QLQ-C30 and QLQ-CLL16 questionnaires take 10–15 minutes to complete altogether. A baseline assessment (prior to any study treatment) as well as subsequent assessements should be conducted as specified in Appendix 1.

The EQ-5D questionnaire is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. The EQ-5D will be utilized in this study for economic modeling. The EQ-5D questionnaire takes 5 minutes or less to complete and should be completed at the same visits as the EORTC QLQ-C30 and QLQ-CLL16.

4.5.1.9 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Residual tumor samples from bone marrow aspirate or lymph node biopsy for DNA, RNA, or protein extraction may be collected before the first study treatment.

The following samples will be collected for identification of dynamic (non-inherited) biomarkers and genetic (inherited) biomarkers:

- Whole blood samples for DNA, RNA, or protein extraction will be collected at first study treatment visit (before any study treatment dosing) and at the end of treatment.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be

told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from study GO28667 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from study GO28667.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 days prior to study treatment initiation, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to initiation of

study treatment may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. PRO assessments should be performed prior to the completion of other study assessments.

See Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at Early Treatment Termination Visit

Patients who discontinue from the study treatment prior to completion of the assigned regimen will be asked to return to the clinic within 4 weeks after the last dose of study treatment for a follow-up visit.

See Appendix 1 for the schedule of assessments performed at Early Treatment Termination Visit.

4.5.2.4 Follow-Up Assessments

After the completion or early termination of study treatment, adverse events should be followed as outlined in Sections 5.5 and 5.6.

Patients who discontinue treatment in the absence of disease progression should still be followed for progression, new anti-CLL therapy and survival according to the protocol schedule.

Patients who have disease progression during study or who have completed 5 years on the study will subsequently have yearly follow-up visits for OS, PD (if not progressed already), and new anti-CLL therapy until end of study. These survival follow-up visits may be conducted by phone.

See Appendix 1 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Unplanned Visits

See Appendix 1 for assessments that are required to be performed in case of an unplanned visit.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsors determine may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsors determine it is in the best interest of the patient
- Patient non-compliance.

4.6.1.1 Discontinuation from Study Drug/Treatment

Patients must discontinue study treatment (venetoclax, bendamustine, rituximab) if they experience any of the following:

- Pregnancy
- Disease progression

Patients who experience toxicity that can be clearly attributed to any particular study drug treatment may discontinue treatment with the specific agent if the toxicity is not tolerable and mitigating strategies are not available or successful. If toxicity cannot be clearly attributed to a single agent and is considered possibly related to the combination treatment, treatment with multiple agents should be discontinued. Patients who discontinue treatment for reasons other than PD should remain on study and continue to have disease assessments per protocol.

Patients in Arm A must discontinue venetoclax permanently if they experience any dose delay of ≥ 4 weeks (except for hepatitis B reactivation) after the last dose (see Section 5.1.5, Table 3). Patients who discontinue venetoclax for reasons other than disease progression should remain on the study and continue to have disease assessments per protocol. Patients in Arm A who discontinue venetoclax for any reason should also discontinue rituximab, although they are to continue evaluation per protocol. Patients in Arm A who discontinue rituximab therapy for toxicity (including anaphylaxis) may continue treatment with single-agent venetoclax after a discussion between the investigator and the Medical Monitor.

Patients in Arm B who experience an anaphylactic reaction must discontinue treatment with the offending agent (see Section 5.1.5 for guidelines on discontinuation of rituximab or dose reduction/modification and discontinuation of bendamustine). Patients in Arm B who discontinue rituximab for toxicity may be eligible to continue monotherapy with

single-agent bendamustine after a discussion between the investigator and the Medical Monitor.

Patients who discontinue study drug/treatment prematurely will be asked to return to the clinic for an Early Treatment Termination Visit (see Section 4.5.2.3) and must undergo follow-up assessments (see Section 4.5.2.4). The primary reason for premature study drug/treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug treatment prematurely will not be replaced.

4.6.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study and Site Discontinuation

The Sponsors have the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsors will notify the investigator if the study is placed on hold, or if the Sponsors decide to discontinue the study or development program.

The Sponsors have the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No ongoing study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Risks Associated with Venetoclax

Phase I/II experience with venetoclax has demonstrated that it is generally well tolerated and toxicities appear to be mostly manageable and/or reversible; however, clinical experience is limited, with 160 patients with CLL/SLL treated with single-agent

venetoclax (study M12-175) or in combination with other agents as of 3 February 2014. Please see the Venetoclax Investigator's Brochure for more information.

5.1.1.1 Tumor Lysis Syndrome

To date, the principal adverse reaction associated with venetoclax in the ongoing single-agent Phase I dose-escalation study M12-175 has been TLS (primarily but not exclusively related to the first dose), and therefore the study has been modified to implement a ramp-up dosing scheme and rigorous TLS prophylaxis (see Section 4.4.1.2).

Experience from study M12-175 has been used to develop a dosing schedule starting at 20 mg/day that is incrementally increased to the target dose for each cohort. Doses that have been safely administered to date from Phase I studies will be used in this study.

TLS, including cases leading to clinical sequelae and death, has been observed at a dose of 50 mg venetoclax, and all patients enrolled in study M12-175 are required to receive hydration and an agent to reduce uric acid as TLS prophylaxis at least 72 hours prior to starting venetoclax treatment. Laboratory testing is required after initial dosing to monitor for metabolic changes and will be used to assess the need for more intensive monitoring and treatment of metabolic abnormalities caused by rapid cell lysis. Please see Section 4.3.2.1.1 and Section 4.4.1.2 for venetoclax dosing instructions and the TLS prophylaxis and monitoring plans, respectively.

5.1.1.2 Cytopenia

Effects on lymphocyte numbers are expected based on the mechanism of action, and modest reductions in neutrophils have been observed with venetoclax therapy in patients. Thrombocytopenia and anemia have been reported with venetoclax in the ongoing single-agent Phase I dose-escalation Study M12-175 and M13-365 that is being conducted in heavily pretreated CLL patients. In certain cases, the condition was preexisting. In this study, blood counts will be monitored closely throughout treatment (see the Schedule of Assessments, Appendix 1). Growth factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infections. Dose interruptions or reductions will be allowed based on toxicity.

5.1.1.3 Infectious Complications

Infections of various types have occurred in patients in the ongoing single-agent Phase I dose-escalation study M12-175. CLL itself is associated with impaired immune function and increased infections, and it is unclear whether or how much the incidence could be increased due to venetoclax treatment. Patients in this study will be closely monitored for infections and prompt therapy will be instituted, as necessary. Patients are allowed to receive concomitant prophylactic anti-infective therapy at the investigator's discretion.

5.1.1.4 Effects on Cardiac Function

Nonclinical studies demonstrated decreases in cardiac function of (contractility and cardiac output) approximately 20% in healthy laboratory animals. No patterns of

adverse events indicating changes in cardiac function have been reported in clinical studies to date. However, the number of patients exposed and the duration of exposure is still relatively low. Patients enrolled in this trial are required to have ECGs and assessments of LVEF at baseline and as clinically indicated afterwards.

5.1.1.5 Effects on Fertility

There is a potential for decreased spermatogenesis. Male patients considering preservation of fertility should bank sperm before treatment with venetoclax and should agree to refrain from donating sperm during the treatment period and for at least 90 days after the last dose of venetoclax. Long-term effects of venetoclax on female reproductive potential are unknown.

5.1.1.6 Drug Interactions

Drug–drug interactions may occur with venetoclax. Please refer to Section 4.4.2 for prohibited and cautionary medications.

5.1.2 Risks Associated with Rituximab Therapy

Please see the prescribing information for rituximab for full information.

5.1.2.1 Infusion-Related Reactions

Patients treated with rituximab are at risk for IRRs. Fatal infusion reactions within 24 hours of rituximab infusion can occur; approximately 80% of fatal reactions occurred with the first infusion. Severe reactions to rituximab typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

5.1.2.2 Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. With rituximab treatment, acute renal failure, hyperkalemia, hypocalcaemia, hyperuricemia, or hypophosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of TLS. Patients treated with venetoclax (Arm A) will receive prophylaxis as described above and in Section 4.3.2.1. Patients randomized to Arm B (BR) who develop evidence of TLS should be treated as clinically indicated.

5.1.2.3 Hepatitis B Reactivation

Hepatitis B reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of rituximab treatment and approximately 1 month after the last dose.

Patients with chronic hepatitis B (HBsAg-positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg-negative and HBcAb-positive) are at a lower risk for reactivation. In a study of 51 hepatitis B carriers with DLBCL who received rituximab, 12% of patients developed evidence of reactivation (Skrabs et al. 2002).

Screen all patients for HBV infection by measuring HBsAg and anti-HBcAb. Patients with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody [HBcAb] and negative HBsAg) may be included if hepatitis B virus (HBV) DNA is undetectable when conducted at a central laboratory. These patients must be willing to undergo monthly HBV DNA testing during therapy and for at least 12 months after the last dose of rituximab. A baseline blood sample followed by monthly testing will be collected to conduct HBV DNA testing at a central laboratory using an assay with a sensitivity of at least 10 IU/mL.

If the HBV-DNA assay becomes positive and is above the World Health Organization's (WHO) cutoff of 100 IU/mL, treatment with venetoclax or R + venetoclax will be held and the patient should be treated (for at least 1 year after the last dose of treatment drug) with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or heptologist for management. Patients may resume venetoclax or venetoclax + R once HBV-DNA levels have decreased to undetectable levels ($<$29 IU/mL).

If the HBV-DNA assay becomes detectable and is 29–100 IU/mL, the patient should be re-tested within 2 weeks. If the assay is still positive, treatment with venetoclax or R + venetoclax will be held and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of study treatment) and immediately referred to a gastroenterologist or heptologist for management. Patients may resume treatment once the HBV-DNA levels decrease to undetectable levels. At the discretion of the investigator, patients may start nucleoside analogue and be referred to a gastroenterologist or hepatologist while the second test in pending.

If a patient's HBV-DNA level exceeds 100 IU/mL while the patient is receiving anti-viral medication, treatment will be discontinued (see Section 5.1.5, Table 4).

HBV reactivation has been reported up to 24 months following completion of rituximab therapy. In patients who develop reactivation of HBV while on rituximab, immediately discontinue rituximab and any concomitant chemotherapy and institute appropriate treatment (see Section 5.1.5 and Table 4). Insufficient data exist regarding the safety of resuming rituximab in patients who develop HBV reactivation.

Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will discontinue study treatment.

5.1.2.4 Progressive Multifocal Leukoencephalopathy

Rare cases of progressive multifocal leukoencephalopathy (PML) have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson et al. 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is extremely rare but should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem-cell transplant. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

5.1.2.5 Cardiac Toxicity

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life threatening. To evaluate baseline risks, patients will be required to undergo assessments of LVEF prior to enrolling in this study. Clinical evidence of cardiac decompensation will be evaluated and managed by the treating physician. The decision to continue a patient on study after developing clinically significant cardiac decompensation will be made by the investigator and the Medical Monitor.

5.1.2.6 Infection

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, Varicella zoster virus, West Nile virus, and hepatitis B and C.

5.1.2.7 Severe Mucocutaneous Reactions

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.

5.1.2.8 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In post-marketing reports of rituximab, the mean time to documented gastrointestinal perforation was 6 days (range, 1–77 days) in patients with NHL.

5.1.3 Risks Associated with Bendamustine

For bendamustine safety monitoring, see Section 4.3.2.3 for monitoring plans and instructions for dose delay and modification of bendamustine. Please see the prescribing information for bendamustine for full information.

5.1.3.1 Myelosuppression

Patients treated with bendamustine are likely to experience myelosuppression. Patients who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The use of myeloid growth factors for the primary and secondary prevention of febrile neutropenia is permitted.

5.1.3.2 Infection

Infection, including pneumonia and sepsis, has been reported. Patients with myelosuppression following treatment with bendamustine are more susceptible to infections. The study physician will treat patients with clinical evidence of infection appropriately. See Section 4.3.2.3 for monitoring plans and instructions for dose delay and modification of bendamustine.

5.1.3.3 Infusion Reactions

Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus, and rash. In rare instances, severe anaphylaxis and anaphylactoid reactions have occurred.

5.1.3.4 Tumor Lysis Syndrome

TLS has been reported in association with bendamustine. Preventive measures include maintaining adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly. Allopurinol may be held on days of bendamustine administration. Patients randomized to Arm B (BR) who develop evidence of TLS should be treated as clinically indicated.

5.1.3.5 Cutaneous Reactions

A number of skin reactions have been reported with bendamustine treatment, including rash, toxic skin reactions, and bullous exanthema. In a study of bendamustine in combination with rituximab, one case of TEN occurred. TEN has been reported for rituximab. Cases of Stevens-Johnson syndrome and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes.

5.1.3.6 Long-Term Stem-Cell Toxicity

Premalignant and malignant diseases, including MDS, myeloproliferative disorders, AML, and bronchial carcinoma, have developed in patients treated with bendamustine.

5.1.3.7 Extravasation of Bendamustine

Erythema, marked swelling, and pain from bendamustine extravasation have resulted in hospitalization.

5.1.3.8 Transfusion-Associated Graft versus Host Disease

Rare cases of transfusion-associated graft versus host disease have been reported following treatment of low-grade B-cell malignancies with purine analogues (i.e., fludarabine or cladribine). The situation with newer purine antagonists such as bendamustine is unclear. Transfusions, if required, should be performed according to national guidelines.

5.1.3.9 Drug Interactions

Certain medications may interact with bendamustine. Caution should be used or alternative treatments should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed. Please see Appendix 9 for a list of medications that are to be excluded or used with caution in patients receiving bendamustine *or venetoclax*.

5.1.4 Risks Associated with Venetoclax and Rituximab Combination Therapy

Preliminary safety (see Section 1.2.2.3.1) and activity (see Section 1.2.2.3.3) data from the ongoing Study M13-365 venetoclax+R supports the risk/benefit assessment for combination therapy. Common hematological and GI toxicities appear to be tolerable and were adequately managed. These common toxicities did not result in any study discontinuation.

5.1.5 Management of Specific Adverse Events

The evaluation of potential treatment-induced toxicity in patients with advanced CLL may be quite difficult and require careful consideration of both the manifestations of the underlying disease, as well as adverse reactions to the therapy under study. Some of the conventional criteria for toxicity are not applicable, especially under circumstances of progressive bone marrow failure from the CLL itself.

Dose modifications for hematologic toxicity in patients with CLL must be made with consideration of the increased frequency of hematologic compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many patients would be considered to have Grade 2–4 hematologic toxicity at presentation.

As a consequence, dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at baseline will be based on the National Cancer Institute–Working Group (NCI-WG) CLL grading scale (see Appendix 12). For patients with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI CTCAE, v4.0 will be used.

Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

Venetoclax + Rituximab Dosage Modifications

Table 3 Dose Modifications for Hematologic Toxicity during the Combination Therapy Period (Venetoclax + Rituximab) and/or Venetoclax Monotherapy

Hematologic toxicity	
Event(s)	**Dose Delay or Modification**
Grade 3 or 4 neutropenia, without infection or fever, and/or Grade 3 or 4 thrombocytopenia, first episode	• Hold venetoclax (and rituximab if neutropenia occurs during Cycles 1–6) • When counts recover to ≤ Grade 2 resume previous doses of venetoclax and rituximab • Administer G-CSF or growth factors for neutropenia as indicated • If patient was not previously receiving prophylactic G-CSF, initiate prophylactic G-CSF for current and all subsequent cycles
Grade 3 or 4 neutropenia with infection and/or fever, first episode	• Hold venetoclax (and rituximab if neutropenia occurs drug Cycles 1–6) until fever and/or infection resolves • Administer G-CSF or growth factors for neutropenia as indicated • When counts recover to ≤ Grade 2 and infection has been fully treated, resume previous doses of venetoclax and rituximab • If patient not previously receiving prophylactic G-CSF, initiate prophylactic G-CSF for current and all subsequent cycles
Recurrent Grade 3 or 4 neutropenia with/without fever and infection despite G-CSF	• Hold venetoclax (and rituximab if neutropenia occurs during Cycles 1–6) for at least 7 days • Administer G-CSF or growth factors for neutropenia as indicated • When counts recover to ≤ Grade 2 and/or platelets are ≥ 75 × 109/L resume venetoclax at one dose level reduction (Table 5) • Reinitiate rituximab at previous dose

Table 3 Dose Modifications for Hematologic Toxicity during the Combination Therapy Period (Venetoclax, Rituximab) and/or Venetoclax Monotherapy (cont.)

Hematologic toxicity (cont.)	
Event(s)	**Dose Delay or Modification**
Grade 4 thrombocytopenia and/or symptomatic bleeding	• Hold venetoclax (and rituximab if event occurs during Cycles 1–6) for Grade 4 thrombocytopenia (platelets < 25,000/μL) or presence of symptomatic bleeding until resolution of bleeding • Platelets may be transfused at the discretion of the investigator • When platelet level rises to ≤ Grade 2 without transfusional support for 5 consecutive days, restart venetoclax and rituximab at previous doses • For a second episode of severe thrombocytopenia and/or symptomatic bleeding, hold venetoclax (and rituximab if event occurs during Cycles 1–6). When platelet level rises to ≤ Grade 2 without transfusional support for 5 consecutive days, restart venetoclax at one dose level reduction (Table 5). Rituximab may be restarted at the previous dose. • For subsequent episodes of severe thrombocytopenia, hold venetoclax (and rituximab if event occurs during Cycles 1–6). When platelet level rises to ≤ Grade 2 without transfusional support for 5 consecutive days, restart venetoclax at one dose level reduction. Rituximab may be restarted at the previous dose. • For recurrent severe thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, consult the Medical Monitor regarding continuation on protocol

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

Table 4 Dose Modifications for Non-Hematologic Toxicity during the Combination Therapy Period (Venetoclax + Rituximab) and/or Venetoclax Monotherapy

Non-hematologic toxicity	
Event(s)	**Dose Delay or Modification**
Grade 4 IRR	Discontinue rituximab permanently. Patients may continue venetoclax.
Grade 3 IRR, first dose	To be managed at investigator's discretion, please note that dose reductions of rituximab are prohibited.
Grade 3 IRR, subsequent episodes	Discontinue rituximab permanently. Patients may continue venetoclax.
Grades 1–2 IRR, first and subsequent episodes	To be managed at investigator's discretion, please note that dose reductions of rituximab are prohibited. Rituximab may be discontinued for patients experiencing recurrent Grades 1–2 IRR.
Grade 3 or 4 tumor lysis syndrome (first episode and subsequent episodes)	Hold all study treatments (venetoclax and rituximab) until TLS resolves. The patient's next dose may be delayed for up to 28 days. Following complete resolution of tumor lysis syndrome and after electrolyte values have been stable without any more treatment for at least 24 hours, if venetoclax was held for 14 days or less, venetoclax (and rituximab if event occurs during Cycles 1–6) may be restarted at the same dose or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status) in conjunction with prophylactic hydration and uricosuric agent; hospitalization for restarting the venetoclax dose may be considered at the discretion of the investigator. Dose must be resumed at one lower dose level if interruption lasted more than 14 days (see Table 5).
Grade 3 or 4 non-hematologic toxicity not specifically described above	Delay venetoclax (and rituximab if event occurs during Cycles 1–6) for a maximum of 28 days. First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax and rituximab. For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at one dose level reduction (Table 5).
Grade 2 non-hematologic toxicity	Delay treatment with venetoclax (and rituximab if event occurs during Cycles 1–6) until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. After resolution, resume full dose of venetoclax and rituximab.
Grade 1 non-hematologic toxicity	No dose reduction or delay.

Table 4 Dose Modifications for Non-Hematologic Toxicity during the Combination Therapy Period (Venetoclax, Rituximab) and/or Venetoclax Monotherapy (cont.)

Non-hematologic toxicity (cont.)	
Hepatitis B reactivation (as evidenced by new detectable HBV-DNA levels)	Detectable HBV-DNA levels between WHO-recommended range of 29 and 100 IU/mL: Re-test within 2 weeks. If still positive, hold venetoclax, or venetoclax and rituximab (if event occurs during Cycles 1–6) and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. At the discretion of the investigation, patients may start the nucleoside analogue and be referred to a gastroenterologist or hepatologist while the second test is pending. HBV-DNA levels at WHO-recommended cutoff of > 100 IU/mL: hold venetoclax or venetoclax and rituximab (if event occurs during Cycles 1–6) and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. Rising HBV-DNA viral load while on an appropriate anti-viral therapy: Discontinue patient from venetoclax and rituximab permanently and refer patient to a gastroenterologist or hepatologist immediately.

IRR = infusion-related reaction; WHO = World Health Organization.

Table 5 Venetoclax Dose Reduction

Venetoclax Current Dose Level	Venetoclax Dose Reduction
400 mg	200 mg
200 mg	100 mg
100 mg	Discontinue venetoclax and rituximab

Gradual dose increase following resolution of toxicity leading to a dose reduction may be considered if the patient is stable for 2 weeks on the lower dose; however, if the toxicity recurs, the patient may continue treatment on the lower dose.

Patients who discontinue venetoclax for toxicity should also discontinue rituximab, although they are to continue evaluation per protocol.

Rituximab Dosage Modifications

There will be no rituximab dose modifications in this study. Patients at high risk for IRRs may, at the investigator's discretion, receive their initial dose of rituximab split over 2 consecutive days (e.g., 125 mg/m^2 on Cycle 1 Day 1 and 250 mg/m^2 on Cycle 1 Day 2).

Rituximab may be temporarily held. Any NCI CTCAE, v4.0 toxicity Grade ≥ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment until resolution to Grade ≤ 1.

Patients in Arm A (venetoclax + R) who discontinue rituximab for rituximab-related toxicity may continue to receive venetoclax. Patients who discontinue venetoclax for toxicity should also discontinue rituximab, although they are to continue evaluation per protocol as described in Section 4.6.1.1.

Patients in Arm B (BR) who discontinue rituximab for rituximab-related toxicity may continue to receive bendamustine as a single agent for the full 6 cycles if deemed to be in the best interest of the patient as assessed by the investigator. Patients who discontinue both bendamustine and rituximab are to continue evaluation per protocol as described in Section 4.6.1.1.

Bendamustine Dosage Modifications

On the first day of each new treatment cycle and before each bendamustine dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). The following dose-reduction rules for bendamustine should be followed (see Table 6 and Table 7).

If toxicities occurred at 70 mg/m^2, reduce dose to 50 mg/m^2; if toxicity occurred at 50 mg/m^2, discontinue bendamustine. If the dose of bendamustine is reduced due to toxicity, it will not be re-escalated later in the study.

Table 6 Bendamustine Dose Reduction

Bendamustine Current Dose Level	Bendamustine Dose Reduction
70 mg/m^2	50 mg/m^2
50 mg/m^2	Discontinue bendamustine

If a patient has disease-related splenomegaly or significant bone marrow involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

Table 7 Dose Modification Guidelines for Bendamustine

NCI CTCAE category	Severity	Dose Modification
Hematologic [a]	Neutrophil <1000/μL on Day 1 of Cycles 2–6	Initiation (Day 1) of Cycles 2–6 should be delayed until the neutrophil count is ≥1000/μL (or returns to baseline level obtained at screening) and the platelet count is ≥75,000/μL.[a] If Day 1 is delayed by more than 2 weeks, then bendamustine should be resumed at the next lower dose level.
	Platelets <75,000/μL on Day 1 of Cycles 2–6	
	Grade 4 neutropenia with fever/infection	Initiation (Day 1) of Cycles 2–6 should be delayed until the neutrophil count is ≥1000/μL without evidence of fever or infection and the platelet count is ≥75,000/μL.[a] Bendamustine should then be resumed at the next lower dose level.
	Grade 4 neutropenia lasting ≥7 days	
	Grade 4 platelets for ≥7 days or a platelet count <10,000/μL at any time	
Nausea, emesis, or diarrhea in the absence of maximal prophylaxis	≥Grade 3	Continue treatment, but with institution of maximum prophylactic therapy, including a 5-HT_3 antagonist for nausea and emesis, and loperamide, or a comparable antidiarrheal agent, for diarrhea. Events of Grade 4 toxicity require holding treatment until resolution of toxicity to ≤Grade 2 with use of maximum prophylaxis.
Nausea, emesis, or diarrhea with maximal prophylaxis	≥Grade 3	Hold bendamustine for up to 2 weeks or until the toxicity returns to ≤Grade 2, and restart at the next lower dose. If treatment is delayed by more than 2 weeks, treatment with bendamustine must be discontinued.
All other toxicities related to bendamustine	≥Grade 3	

5-HT_3 = 5-hydroxytryptamine 3; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] If patients have disease-related splenomegaly or significant bone marrow involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsors immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsors immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- Suspected transmission of an infectious agent by the study drug
- Grade >3 TLS and IRR

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsors in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient’s medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug, or 90 days after last dose of rituximab, whichever is longer. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE, v4.0 will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE, v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (last accessed: 22 April 2013)

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment–related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after rituximab and/or bendamustine infusion and that are judged to be related to the respective infusion should be captured as a diagnosis rather than individual signs and symptoms (e.g. “infusion-related reaction” or “injection-site reaction” or “anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For all other adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously

reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting or diarrhea results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting or diarrhea results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

In this study, certain abnormal values may not qualify as adverse events. Hematologic parameters should be evaluated as described in Table 3 and Table 4 and in Appendix 12. G-CSF used as prophylaxis would not be considered an adverse event but should be reported as a concomitant medication.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium" as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsors immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of CLL should be recorded only on the Study Completion/Early Discontinuation eCRF. All other deaths during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the

cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

During follow-up visits occuring after the adverse event reporting period, deaths attributed to progression of CLL should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the Medical History/Surgical History.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Lack of Efficacy or Worsening of CLL

Events that are clearly consistent with the expected pattern of progression of the underlying disease (such as transformation to more aggressive histology) should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for monitoring for potential TLS)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care.

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Paper or electronic questionnaires may be used for this study. In the event paper is used, instructions on the PRO questionnaires will include a disclaimer to let patients know that the site staff will not be reviewing the answers to the questionnaire and therefore patients should alert the site staff about any problems they are having. Site staff will review PRO questionnaires for completeness ONLY. If it is noted that the patient has written any words on the PRO instrument that is not a predefined response (e.g., comments in the margin of the questionnaire or comments in an open text field), site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsors to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsors immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsors within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsors immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information (North, Latin, and South America)

Medical Monitor: [redacted]

Telephone No.: [redacted]

Alternate Telephone No.: [redacted]

[redacted] **Medical Responsible Contact Information (Rest of World)**

Medical Advisor-based in France: [redacted] M.D.

Telephone No.: [redacted]

Medical Advisor-based in Italy: [redacted] M.D.

Telephone No.: [redacted]

Medical Advisor-based in Singapore: [redacted] M.D.

Telephone No.: [redacted]

[redacted] Medical Emergency Contact Center: [redacted]

Alternate Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Contact, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to AbbVie/Roche Safety Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed directly to [redacted] (AbbVie/Roche Safety Management designee) immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug (or within 90 days of the last dose of rituximab). A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to AbbVie/Roche Safety Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed faxed directly to [redacted] (AbbVie/Roche Safety Management designee) immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after completing treatment with venetoclax or 180 days after the last dose of rituximab. Male patients who received study treatment should not attempt to father a child until end of study or for 1 year after the last dose of rituximab. A Pregnancy Report

eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsors consider spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsors immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (see Section 5.3.1) if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to [redacted] (AbbVie/Roche Safety Management or designee) using the paper Serious Adverse Event Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsors will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsors will assess the expectedness of these events using the following reference documents:

- Venetoclax Investigator's Brochure
- Local prescribing information for rituximab
- Local prescribing information for bendamustine

The Sponsors will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsors as needed.

Certain adverse events (e.g., know consequences of the underlying disease or common co-morbidities in the study population) are anticipated to occur in the study population (CLL) at some frequency independent of drug exposure and will be excluded from expedited reporting by the Sponsor to applicable health authorities. Although exempt

from expedited reporting to certain health authorities and ECs/IRBs as individual cases, these Serious Adverse Events and Adverse Events of Special Interest, as defined in Section 5.4.2, must be reported by the site/investigator expeditiously to the Sponsors within 24 hours of the site becoming aware of the event. These events are listed in Appendix 13. These adverse events may occur alone or in various combinations and are considered expected for reporting purposes for this protocol. The list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms associated with these events.

The iDMC will monitor the safety events in this study. Any recommendation from the iDMC during the study that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Details of the analyses presented in this section will be provided in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint of PFS was used to determine the sample size for the study. Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Two-sided log-rank test at the 0.05 level of significance
- 80% power to detect a hazard ratio (HR) for venetoclax + R versus BR of 0.66, corresponding to an approximate median improvement of 15.2 months to 23 months (34% reduction in risk of a PFS event)
- Exponential distribution of PFS
- An annual dropout rate of 5%
- One interim analysis for efficacy

With these assumptions, 186 PFS events are required to achieve 80% power for the primary analysis of PFS in all patients for detecting a trend in favor of venetoclax + R arm over BR arm (HR $\leq$ 0.66). In total, it is planned to enroll approximately 370 patients across 2 arms, randomized with 1:1 ratio. It is expected that, after a 9-month enrollment ramp-up, 24 patients per month will be recruited, and the total enrollment is expected to take approximately 20 months.

An interim analysis is planned when approximately 140 investigator-assesed PFS events have occurred in both treatment arms combined (75% of the 186 events required for the final primary efficacy analysis

The minimum detectable difference at the final analysis approximately corresponds to a HR of 0.75.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, eligibility violations, study drug administration, and patient disposition will be summarized by treatment arm in all randomized patients and by 17p deletion status. A summary of patient disposition will include whether treatment was completed or discontinued early and the reason for early treatment discontinuation. Descriptive statistics will be used in evaluating the conduct of the study.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, and baseline ECOG Performance Status, will be summarized by treatment arm in all randomized patients. Descriptive statistics will be used in evaluating treatment group comparability.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard iwCLL guidelines [Hallek et al. 2008]), or death from any cause, whichever comes first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of the last disease assessment. If no disease assessments were performed after the baseline visit, PFS will be censored at the time of randomization + 1 day. Although the primary efficacy endpoint is investigator-assessed PFS, PFS based on IRC assessments will also be analyzed to support the primary analysis. In the United States, IRC-assessed PFS will be the basis of regulatory decisions.

The primary analysis of the study will test the equality of PFS distributions for the venetoclax and rituximab combination (venetoclax + R, Arm A) and the bendamustine and rituximab combination (BR; Arm B), as follows:

$$H_0: PFS_{venetoclax + R} = PFS_{BR}$$
versus
$$H_1: PFS_{venetoclax + R} \neq PFS_{BR}$$

Treatment comparison will be made using a two-sided stratified log-rank test (0.05 significance level, appropriately adjusted for an interim analysis) stratified by 17p deletion status (yes or no), risk status (high or low risk), and geographic region (United States/Canada, Australia/New Zealand, Western Europe, Central and Eastern Europe, Asia, or Latin America). If the null hypothesis is rejected and the observed HR is favorable for the venetoclax + R combination, then it is shown that venetoclax + R has a statistically significantly longer PFS than BR. The Kaplan–Meier curve will provide a

visual description of the differences across treatment arms. Estimates of the treatment effect will be expressed as HRs through use of a stratified Cox proportional-hazards analysis, including 95% confidence intervals.

The following sensitivity analyses for PFS will also be performed:

- An unstratified log-rank test will be performed.
- PFS analyses will be performed with censoring at the initiation of non-protocol–specified anti-CLL therapy to assess potential confounding of the treatment effect estimates by subsequent therapy.
- PFS analyses will be performed with censoring death or disease progression after more than one missed response assessment at the date of the last adequate response assessment.

Details will be outlined in a Statistical Analysis Plan.

6.4.2 Secondary Efficacy Endpoints

If the study meets its primary endpoint of prolonging PFS assessed by the investigator in all randomized patients, then formal statistical tests of *specific key secondary efficacy endpoints will be performed.* To adjust for multiple testing of the primary and key secondary efficacy endpoints, thereby controlling the overall type I error rate at a 2-sided significance level of 0.05, a fixed sequence testing procedure will be used (Westfall and Krishen 2001). *Additional secondary endpoints will not be tested formally. Further details of the fixed sequence testing will be described in the Statistical Analysis Plan.*

Secondary efficacy outcome measures include:

- *Investigator-assessed PFS in patients with 17p deletion per central laboratory Fish test*
- *IRC-assessed PFS in patients with 17p deletion per central laboratory detection*
- *Investigator-assessed best OR rate, CR, CRi, nPR, and PR rates*
- *IRC-assessed best OR rate, CR, CRi, nPR, and PR rates*
- OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit as assessed by the investigator.
- OR, CR, CRi, nPR, and PR rates at end of combination treatment response visit, as determined by the IRC.
- *OS, defined as the time from the date of randomization to the date of death from any cause. Patients who were not reported as having died at the time of the analysis will be censored at the date when they were last known to be alive as documented by the investigator.*
- EFS, defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-CLL treatment. *If the specified event*

(disease progression/relapse, death, start of a new anti-CLL treatment) does not occur, patients will be censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS will be censored at the time of randomization.

- DOR, defined for patients with a best OR of CR, CRi, nPR, or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse as assessed by the investigator or death from any cause. *For patients achieving a response who have not progressed, relapsed, or died at the time of analysis, DOR will be censored on the date of last response assessment. Patients who have never had responded will not be included in this analysis.*
- TTNT, defined as the time from randomization to start of new non-protocol anti-*CLL* therapy or death from any cause. *For patients who have not received the next anti-CLL treatment or died at the time of analysis, TTNT will be censored at the date when the patient was last known to be alive without having received additional anti-lymphoma treatment.*
- MRD response rate (determined as the proportion of patients with MRD negativity) at End of Combination Treatment Response Visit as measured at a central laboratory on peripheral blood and/or bone marrow samples

Time-to-event endpoints such as OS, EFS, and TTNT will be analyzed using the same statistical methods described for the primary analysis of PFS.

Time-to-event analysis of DOR will incorporate data only from the subset of patients in both treatment arms that achieved a CR, CRi, nPR, or PR status. As this a nonrandomized comparison, a formal statistical test will not be conducted, and the results will only be summarized by the treatment arm estimates and confidence intervals.

Response rates in the treatment groups will be compared using stratified Cochran–Mantel–Haenszel (CMH) tests. Stratification factors are identical to those used for the primary endpoint. Rates and 95% confidence intervals will be reported for each treatment group.

6.5 SAFETY ANALYSES

Safety endpoints include adverse events, serious adverse events, and adverse events of special interest. The safety analyses will include all randomized patients who received at least one dose of study treatment (venetoclax, rituximab, or bendamustine), with patients grouped according to the treatment actually received.

Treatment exposure will be summarized, including the number of cycles received by each patient, and the cumulative dose will be summarized by treatment arm.

Verbatim descriptions of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. All adverse events occurring during or after the first treatment will be summarized by treatment arm and NCI CTCAE grade. In addition, all serious adverse events will be summarized.

Deaths reported during the study treatment period and those reported after treatment completion/discontinuation will be summarized by treatment arm.

Adverse events leading to early treatment discontinuation and early study withdrawal will be summarized by arm and reason.

Laboratory data with values outside of the normal ranges will be identified. Additionally, select laboratory data will be summarized by treatment arm and grade using the NCI CTCAE. Of note, abnormal laboratory data that are clinically significant will be reported as adverse events and summarized in the adverse event tables.

Vital signs and other physical findings will be summarized by treatment arm.

6.6 PHARMACODYNAMIC ANALYSES

The pharmacodynamics endpoint in this study is serial assessment of B- and T-cell lymphocyte subsets by flow cytometry.

The exploratory pharmacodynamic biomarker analyses will include patients with at least one predose and/or one post-dose biomarker assessment, with patients grouped according to the treatment actually received.

Blood samples for biomarker assessments will be assayed using analytically qualified methods (e.g., immunohistochemistry, ELISA, quantitative real-time PCR, and fluorescence-activated cell sorting).

6.7 PHARMACOKINETIC ANALYSES

Individual plasma concentrations of venetoclax will be tabulated after appropriate grouping, summarized (e.g., mean, standard deviation, coefficient of variation, median, minimum, and maximum), and plotted.

Population PK methods will be used to characterize the pharmacokinetics of venetoclax in this study in conjunction with appropriate historical data. Apparent clearance, apparent volume of distribution, and other appropriate PK parameters of venetoclax may be calculated and summarized as data allow.

Potential correlations of exposure with dose, demographics, pharmacodynamic variables, safety, and efficacy outcomes may be explored as warranted by the data. The results from the population PK analysis may be reported separately from the Clinical Study Report.

At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of venetoclax.

6.8 PATIENT-REPORTED OUTCOME ANALYSES

The PRO endpoints in this study are:

- To compare interference and tolerability of treatment-related symptoms in patients treated with venetoclax+R versus BR using the MDASI questionnaire
- To evaluate changes from baseline disease-related symptom scores using the MDASI and EORTC QLQ-C30 and QLQ-CLL16 questionnaires
- To evaluate time to disease-related symptom progression using EORTC QLQ-C30 and QLQ-CLL16
- To evaluate interference of treatment and disease-related symptoms on QoL using the MDASI questionnaire

Scoring for the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 questionnaires will be based on their corresponding user manuals (Fayers et al. 1999, Cleeland et al. 2000). For the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales with more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

Summary statistics of the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16 scales and their changes from baseline will be calculated at each assessment timepoint for both study arms. Analysis details of these patient-reported outcomes will be provided in the Statistical Analysis Plan.

Disease-related symptom progression will be measured by EORTC QLQ-C30 and EORTC QLQ-CLL questionnaires. Time-to-event Kaplan–Meier analysis on CLL symptoms will be used to demonstrate the time from first treatment to worsening in disease-related symptoms. An event is a change in symptom score by 10 points or more as defined as being clinically important.

6.9 HEALTH ECONOMIC ANALYSIS

Health economic data, as assessed by the EQ-5D, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D assessment that generate a score. Scores at baseline and change from baseline scores for each timepoint will be quantified using descriptive statistics.

The results from the health economic data analysis may be reported separately from the Clinical Study Report.

6.10 EXPLORATORY ANALYSES

Relationship between various baseline markers and clinical outcome parameters in patients from both arms of the study (including CLL prognostic markers, pro- and anti-apoptotic RNAs and proteins in CLL cells, and pharmacogenomics variables) will be assessed using appropriate laboratory measures.

6.11 INTERIM ANALYSES

One interim analysis is planned during the conduct of the study to assess efficacy and safety of venetoclax + R compared with BR and to allow for release of the results earlier than the planned final analysis in case of significant difference in treatment effect in favor of venetoclax + R.

The interim analysis will be performed when approximately 140 investigator-assessed PFS events have occurred in both treatment arms combined (75% of the 186 events required for the final primary efficacy analysis). The stopping boundary follows a unified family with parameter of P = 2 (Kittelson and Emerson 1999). Based on 140 events, the duration of PFS will be tested at the interim analysis, approximately corresponding to a 2-sided p-value of 0.0026 (HR of 0.60). If the number of events is not exactly 140 by the time of the analysis, then the boundary will be updated to reflect the number of events

The iDMC will evaluate efficacy and safety data at the interim analysis and recommend if the study result should be released early. Summaries and analyses will be prepared by the iDCC and presented by treatment arm for the iDMC's review (see Section 3.1.2).

Both investigator-assessed PFS analysis and a corresponding analysis on the basis of IRC-assessed PFS will be conducted in this interim analysis. The same stratification factors as specified in the primary efficacy endpoint analysis will be used. If the p-value of the stratified 2-sided log-rank test is ≤ 0.0026 (approximately corresponding to a HR of 0.60) for both investigator- and IRC-assessed PFS analysis and the observed HR is favorable for the venetoclax+ R combination treatment, the study will have shown statistically significantly longer duration of PFS in the venetoclax + R arm and will have met its primary efficacy endpoint. The results are expected to be presented to the health authorities for potential registrational purposes.

The final primary efficacy analysis will be performed when approximately 186 investigator-assessed PFS events have been observed, where PFS will be tested at the significance level of approximately 0.0498 (two-sided), corresponding to detecting an HR of ≤ 0.75 or less. If necessary, the statistical test level will be adjusted to incorporate the alpha spent at the interim analysis so that the overall type I error rate will be maintained at the 2-sided 0.05 level.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsors will supply electronic eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data and any other electronic data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsors will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsors, and the Sponsors' standard procedures will be used to handle and process the electronic transfer of these data.

Electronic CRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

Electronic patient-reported outcome (ePRO) data will be collected using an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The ePRO device data are available for view access only via secure access. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsors will have view access only. System backups for data stored by the Sponsors and records retention for the study data will be consistent with the Sponsors' standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic CRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsors and should be handled in accordance with instructions from the Sponsors.

All eCRFs should be completed by designated, trained site staff. Electronic CRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an ePRO device to capture PRO data. The data will be transmitted via internet automatically after entry to a centralized database at the ePRO vendor. The data can be reviewed by site staff via secure access to an internet server.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsors. Written notification should be provided to the Sponsors prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsors' sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsors or their designee must review and approve any proposed deviations from the Sponsors' sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Informed Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Informed Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Informed Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Informed Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Informed Consent Forms for continued participation in the study.

A copy of each signed Informed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Informed Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Informed Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the

local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsors maintain confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsors with sufficient, accurate financial information in accordance with local regulations to allow the Sponsors to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

Approximately 150 international centers will participate in this study to enroll up to approximately 370 patients. Data will be recorded via an EDC system from [redacted]) using electronic Case Report Forms (eCRFs; see Section 6.6). Central laboratories will be used for the analyses of and/or management of pharmacodynamic, genotyping, and tissue samples. An IxRS will be used for patient registration, patient number, and dose assignment.

This trial is being conducted globally under a collaboration agreement between F. Hoffmann–La Roche, Ltd. and AbbVie, Inc. F. Hoffmann–La Roche, Ltd. and AbbVie, Inc. will act as co-sponsors of the trial in the United States. AbbVie GmbH & Co. KG (Germany) will act as the sponsor of the trial for participating countries in the European Union. In countries where an AbbVie entity is the sole sponsor, Genentech and a CRO will manage the study and carry out certain sponsor responsibilities delegated to Genentech by AbbVie, in accordance with applicable laws/regulatory requirements.

AbbVie, Inc. is the holder of the U.S. IND under which this study is being conducted. AbbVie will file all clinical trial applications for this study outside of the United States.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsors prior to submission. This allows the Sponsors to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsors will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsors will generally

support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsors. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Patients Randomized to Arm A (Venetoclax+R)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Informed consent	X																			
Demographic data [a]	X																			

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
General medical history and baseline conditions	X																			

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Concomitant medications, adverse events, and compliance assessment	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
ECOG Performance Status	X	X					X				X			X	X	X	X	X	X	
Vital signs [b]	X	X[b]	X[b]	X[b]	X[b]	X[b]	X	X	X	X	X			X	X	X	X	X	X	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Height (at screening only), weight, calculation of BSA	X						X		X	X	X			X	X	X	X	X	X	
Physical examination[c]	X																			

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Targeted physical examination		X	X	X	X	X	X				X			X	X	X	X	X	X	
Assessment of LVEF [d]	X															X	X			
CLL response assessment [e]	X						X				X			X	X	X	X	X	X	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
CT (or MRI) scan [e]	X													X[e]				X[e]	(X)	
Bone marrow aspirate and biopsy (including flow cytometry or IHC) [f, g]	X													(X)		(X)	(X)	(X)	(X)	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Pregnancy test [h]	X	X					X				X				X			X	X	
Viral serologies [i]	X																			
HBV DNA on PCR (for applicable patients)[j]	(X)						(X)				(X)				(X)	(X)	(X)	(X)	(X)	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Hospitalization [k]		(X)	(X)	(X)	(X)	(X)	(X)													
Hematology [l]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	X	X	X				X	X	X	X	X	
Coagulation	X																			
Serum chemistry [l]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	X	X	X				X	X	X	X	X	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
B–, T–, and NK–cell markers (flow cytometry) [o]	X													X		X	X	X	X	
Urinalysis [p]	X																			
Serum QIG [q]	X													X		X	X	X	X	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
CLL prognostic factors (including CLL FISH for 17p) [r]	X																			
MRD on peripheral blood [rs]	X													X		X	X	X	X[q]	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Blood and bone marrow samples for Bcl-2 family (RNA, flow cytometry) [t]	X															(X)	(X)	(X)	(X)	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Blood sample for in vitro sensitivity to venetoclax [t]		X																		
Blood sample for Bcl-2: Bim analysis [t]							X													

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Tumor cells for Bcl-2 family by IHC (formalin fixed tissue) [u]	X																			

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Optional Roche Clinical Repository samples [v]		(X)														(X)	(X)			
venetoclax [w]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rituximab [x]							X	(X)			X				X					

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
MDASI [y]		X					X		X	X	X	X	X							
EORTC QLQ-30 and CLL-16 [z]		X					X				X				X	X	X	X	X	
EQ-5D [z]		X					X				X				X	X	X	X	X	
ECG [aa]	X																			

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
PK sampling [bb]							X								X[bb]					
B Symptoms	X	X					X				X			X	X	X	X	X	X	
MRD in bone marrow[cc]	X[f]																	(X)	(X)	

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Anti-CLL therapy[dd]																	X		X	X

Appendix 1
Schedule of Assessments (cont.)

Arm A (Venetoclax +R)	Screening	Venetoclax Ramp-up Period					Combination (Venetoclax+R) Therapy									Venetoclax Monotherapy/Follow-Up				
							Cycle 1				Cycles 2–3			Interim Response Assessment	Cycles 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-Up Visits
Day		1	8	15	22	29	1	2	8	15	1	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (±days)	Day -28 to -1	+1	+1	+1	+1	+1	±1	0	±1	±1	±3	±1	±1		±3	±7	±7	±7	±7	±30
Survival status/ disease progression																				X

Appendix 1
Schedule of Assessments (cont.)

BSA = body surface area; C = cycle; C4D1 = Cycle 4 Day 1; C4D1 = Cycle 6 Day 1; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ C-30/CLL16 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30/ Chronic Lymphocytic Leukemia Module 16 questionnaires; EQ-5D = EuroQol's EQ-5D questionnaire; FISH = fluorescence in situ hybridization; HBcAb = serum immunoglobulin G antibody directed at hepatitis B core antigen; HBsAg = hepatitis B virus surface antigen; IgG anti-Hep C Ab = serum antibody directed against hepatitis C virus; IHC = immunohistochemistry, IV = intravenous; IVRx = interactive voice response solution; LVEF = left ventricular ejection fraction; MDASI = M. D. Anderson Symptom Inventory; MRD = minimal residual disease; MRI = magnetic resonance imaging; NK = natural killer cell; PD = progressive disease; PK = pharmacokinetic; PO = per os, orally; PR = partial response; PRO = patient-reported outcome; QIG = quantitative immunoglobulin (including serum levels of IgA, IgG and IgM); R = rituximab; TLS = tumor lysis syndrome.

Note: (X) indicates assessments that may be performed but are not required, as determined by the investigator

[a] Patient age, sex, race, self-reported ethnicity.

[b] Vital signs will include measurements of temperature, heart rate, systolic and diastolic blood pressure. Vital signs should be collected at all times of chemistry blood draws.

[c] Complete physical examination is required at screening; targeted physical examination for all subsequent visits. Complete physical examination includes all systems of the body as described in the body of the protocol. Targeted physical examinations should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, lymphatics [including spleen], and gastrointestinal [including liver], and those associated with clinical signs/symptoms).

[d] Assessment of LVEF by either echocardiogram or multigated acquisition (MUGA) scan after screening is at the discretion of the investigator.

[e] All patients must have clinical response assessments (including targeted physical examination and laboratory examinations) at interim response assessment (within 14 days of Cycle 4 Day 1), and 4 weeks after Day 1 of the last cycle. All patients must have a baseline CT scan (or MRI if CT is contraindicated) of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. A follow-up scan must also be performed at the interim response assessment (within 14 days of Cycle 4 Day 1) visit and for final response assessment following completion of combination therapy or early termination (2–3 months after Day 1 of the last treatment cycle). Targeted physical examination and laboratory examinations should be repeated to confirm that patients are still in response prior to confirmatory CT or MRI scan. Imaging evaluations at subsequent study visits are only required to confirm a new response (i.e., to confirm a new PR or CR). Imaging evaluations must be performed within 2 weeks for patients who meet the clinical criteria for PD (i.e., increased or de novo enlargement of liver, spleen, or lymph nodes on physical examination) in the absence of laboratory or histopathologic criteria for PD. MRI scans of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used instead of CT scans in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis. If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study.

[f] A bone marrow examination must be performed at screening. For those patients who have achieved a CR or cytopenic CR (including a CT scan indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR at least 8 weeks following the initial clinical assessment of CR. If the CR occurs at the interim response assessment visit, the bone marrow aspirate and biopsy to confirm that CR should be performed around Cycle 6 (at least 8 weeks following the interim response assessment visit). If the bone marrow examination confirms a CR, then a repeat bone marrow at the end of combination response visit is not needed. Otherwise, a subsequent bone marrow aspirate and biopsy would be required to confirm a new CR.

[g] A bone marrow aspirate should be obtained for MRD assessment in all responding patients (CR or PR).

[h] Required for all women of reproductive potential (see inclusion criteria).

[i] HBsAg, IgG anti-HBcAb, and Hep C Ab serology (also HCV RNA by polymerase chain reaction if the patient is HCV antibody positive) required.

[j] For hepatitis B core antibody–positive patients, the HBV DNA titer needs to be determined using real-time PCR monthly until at least 12 months after the last rituximab dose. Note that during the venetoclax monotherapy/follow-up period, HBV DNA titer should be performed monthly and the results reviewed by the investigator or designee. The patient does not need to have any other procedures besides this laboratory test between the 12-week follow-up visits unless clinically indicated.

[k] Refer to Section 4.4.1.2 for hospitalization and prophylaxis measures for TLS.

[l] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count), platelet count, absolute neutrophil count, absolute lymphocyte count, and percent or absolute differential counts (e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells.

[m] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen or urea (when BUN not available), creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, and uric acid. All scheduled blood draws may be drawn up to 72 hours prior to the next planned evaluation.

[n] Serum hematology and chemistries should be drawn at the specific timepoints as descr bed in detail in Section 4.4.1.2 .

[o] Peripheral blood lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16, and CD56) measured by flow cytometry are required at screening, interim response assessment (within 14 days of Cycle 4 Day 1), early termination or end of combination treatment, 12 weeks after Day 1 of the last cycle of combination therapy, and every 12 weeks thereafter.

[p] Consists of specific gravity, pH, blood, protein, glucose, ketones, and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[q] QIG: quantitative immunoglobulin (including serum levels of IgA, IgG and IgM).

[r] Patients will have the following samples drawn at screening: serum for β2-microglobulin, whole blood for IgV_H mutational status, p53 and other prognostic mutations, and interphase FISH for chromosomal abnormalities including 17p-, 11q-, 13q-, and trisomy +12. Sample will be taken for both local and central testing of 17p deletion by FISH. In the event a local 17p FISH test is not available, the central test results may be used for randomization.

[s] MRD samples in peripheral blood collected at baseline, within 14 days of C4D1 (interim response assessment), completion of Combination Therapy/Early Treatment Termination visit (if applicable), End of Combination Treatment Response Visit, and at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 months after completion of combination therapy, or at any visit during follow-up where a patient has a response (PR or CR status)will be measured at a central laboratory.

[t] Whole blood predictive biomarker sample is required for all patients at screening and at time of progression (early termination if applicable) or at end of treatment, one tube each for protein and RNA analysis of Bcl-2 family members. A predictive bone marrow aspirate sample (1 mL each for protein and RNA analysis) must be drawn for all patients at screening. Aspirate samples should be split from samples obtained for International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute Working Group or International Working Group criteria assessment whenever poss ble. If aspirate sample is limiting, then protein should be prioritized over RNA sample. Please note that a bone marrow biopsy and aspirate is not required at the time of progression (unless it is needed to confirm or rule out PD); however, if it is performed then a predictive bone marrow biomarker sample should also be drawn. Predictive biomarker sample will be used for assessment of Bcl-2 family and other relevant markers by RNA and flow in the blood and

bone marrow. Additional biomarker assessments will include a blood sample that will be collected at Cycle 1 Day1 predose and 4-hours post-dose for Bcl-2:Bim complex by protein in blood and a blood sample collected predose at Day 1 of the ramp-up period for venetoclax in vitro sensitivity.

[u] If formalin fixed specimen of bone marrow biopsy (also including lymph node or other biopsies) is collected at screening by the site per standard clinical assessment of the patient, a sample should be provided for IHC analysis of Bcl-2 family.

[v] Residual tumor specimens are requested at screening and optional blood samples are requested at Day 1 of ramp-up period and at the end of combination therapy or End of Combination Treatment/Early Treatment Termination Visit for collection and storage at the Roche Clinical Repository.

[w] For patients randomized to Arm A, venetoclax will be taken daily by mouth starting on Day 1 through the end of study. As described in Section 4.3.2.1 , there will be a 5 week venetoclax ramp-up period when patients will start with a 20 mg dose on Day 1 for a week. Patients will increase to 50 mg on Day 8and subsequently increase the dose weekly to reach the dose of 400 mg for the study. Patients will continue venetoclax at 400 mg PO daily with concurrent rituximab for 6 cycles of 28 days each. Patient with no evidence of progression will continue single agent venetoclax (400 mg PO daily) until progressive disease, unacceptable toxicity, or for a maximum of 2 years.

[x] On Day 1 of Cycle 1, patients will receive rituximab 375 mg/m^2 IV followed by rituximab 500 mg/m^2 IV on Day 1 of Cycles 2 through 6. Investigators will have the option of administering the rituximab dose for Day 1 Cycle 1 over 2 days (e.g., 100 mg IV on Day 1, Cycle 1 followed by the remainder of the 375 mg/m^2 dose on Day 2 Cycle 1).

[y] The MDASI questionnaire will be completed at home on the specified days. An interactive voice response solution (IVRx) will be used to capture the MDASI questionnaire data.

[z] Patients should complete the questionnaires prior to study drug administration and any other study assessments. PRO assessments should be performed prior to progression, at the time of progression, and at the first assessment after progression.

[aa] An ECG is required at screening only as clinically indicated.

[bb] PK data will be collected for patients randomized to Arm A only. Unscheduled PK sample will be collected from patients developing laboratory or clinical evidence of TLS. PK samples are to be collected on Day 1 of Cycle 1 and on Day 1 of Cycle 4 at the timepoints described in Appendix 2.

[cc] A bone marrow aspiration should be obtained for MRD assessment in the bone marrow in all responders (CR＋PR) at the End of Combination Treatment Response Visit or any time after, if the patient becomes a responder. A sample of the bone marrow examination performed at Screening will also be used to assess MRD in the bone marrow.

[dd] Assessment is required but may not be applicable.

Appendix 1
Schedule of Assessments (cont.)

Patients Randomized to Arm B (BR)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
Informed consent	X															
Demographic data [a]	X															
General medical history and baseline conditions	X															

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
Concomitant medications, adverse events, and compliance assessment	X	X	X	X	X	X	X			X	X	X	X	X	X	
ECOG Performance Status	X	X				X					X	X	X	X	X	
Vital signs [b]	X	X	X	X	X	X	X				X	X	X	X	X	

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
Height (at screening only), weight and calculation of BSA	X	X	(X)	X	X	X					X	X	X	X	X	
Physical examination [c]	X															
Targeted physical examination		X		X	X	X					X	X	X	X	X	
Assessment of LVEF	X															

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
CLL response assessment [d]	X					X				X	X	X	X	X	X	
CT (or MRI) scan [d]	X									X[d]				X[d]	(X)[d]	
Bone marrow aspirate and biopsy (including flow cytometry or IHC) [e]	X									(X)		(X)	(X)	(X)	(X)	

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
Pregnancy test [f]	X	X				X					X			X		
Viral serologies [g]	X															
HBV DNA on PCR (for applicable patients) [h]	(X)	(X)				(X)					(X)	(X)	(X)	(X)[h]	(X)[h]	
Hematology [i]	X	X	X	X	X	X	X				X	X	X	X	X	
Coagulation	X															
Serum chemistry [j]	X	X	X	X	X	X	X				X	X	X	X	X	

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
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Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
B–, T–, and NK–cell markers (flow cytometry)[k]	X									X		X	X	X	X	
Urinalysis [l]	X															
Serum QIG	X									X		X	X	X	X	
CLL prognostic factors (including CLL FISH for 17p) [m]	X															

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
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Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
MRD on peripheral blood [n]	X									X		X	X	X	X^n	
Blood and bone marrow samples for Bcl-2 family (RNA, flow cytometry) [o]	X											(X)	(X)	(X)	(X)	
B Symptoms	X	X				X				X	X	X	X	X	X	
Blood sample for Bcl-2: Bim analysis[o]		X														

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
Tumor cells for Bcl-2 family by IHC (formalin fixed tissue)[p]	X															
Optional Roche Clinical Repository samples [q]		(X)										(X)	(X)			
Rituximab [r]		X	(X)			X	(X)				X					
Bendamustine [s]		X	X			X	X				X					

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
MDASI [t]		X		X	X	X		X	X							
EORTC QLQ-30 and CLL-16 [u]		X				X					X	X	X	X	X	
EQ-5D [u]		X				X					X	X	X	X	X	
ECG [x]	X															
MRD in bone marrow[y]	X													(X)	(X)	
Anti-CLL therapy[z]													X		X	X

Appendix 1
Schedule of Assessments (cont.)

Arm B (BR)	Screening	Combination (BR) Therapy										Observation and Follow-up				
		Cycle 1				Cycles 2–3				Interim Response Assessment	Cycle 4–6	Completion of Combination Therapy	Early Treatment Termination (if applicable)	End of Combination Treatment Response Visit	Follow-up Visits	Survival Follow-up Visits
Day		1	2	8	15	1	2	8	15	Within 14 days of C4D1	1	4 weeks after Day 1 of C6D1	4 weeks after last dose of study treatment	12 weeks (earliest 8 weeks) after Day 1 of last cycle of combination therapy	Every 12 weeks until 3 years, then every 24 weeks until 5 years	Every year after 5 years on study or disease progression
Visit Window (± days)	Day -28 to -1	±1	±1	±1	±1	±3	±1	±1	±1		±3	±7	±7	±7	±7	±30
Survival status/ disease progression																X

BSA = body surface area; C = cycle; C1D1 = Cycle 1 Day 1; C4D1 = Cycle 4 Day 1; C6D1 = Cycle 6 Day 1; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ C-30/CLL16 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30/ Chronic Lymphocytic Leukemia Module 16 questionnaires; EQ-5D = EuroQol's EQ-5D questionnaire; FISH = fluorescence in situ hybridization; HBcAb = serum immunoglobulin G antibody directed at hepatitis B core antigen; HBsAg = hepatitis B virus surface antigen; IgG anti-Hep C Ab = serum antibody directed against hepatitis C virus; IHC = immunohistochemistry, IV = intravenous; IVRx = interactive voice response solution; LVEF = left ventricular ejection fraction; MDASI = M. D. Anderson Symptom Inventory; MRD = minimal residual disease; MRI = magnetic resonance imaging; NK = natural killer cell; PD = progressive disease; PK = pharmacokinetic; PO = per os, orally; PRO = patient-reported outcome; QIG = quantitative immunoglobulin (including serum levels of IgA, IgG and IgM); R = rituximab; TLS = tumor lysis syndrome.

Appendix 1
Schedule of Assessments (cont.)

Note: (X) indicates assessments that may be performed but are not required, as determined by the investigator.

[a] Patient age, sex, race, self-reported ethnicity.

[b] Vital signs will include measurements of temperature, heart rate, systolic and diastolic blood pressure.

[c] Complete physical examination is required at screening; targeted physical examination for all subsequent visits. Complete physical examination includes all systems of the body as descr bed in the body of the protocol. Targeted physical examinations should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, lymphatics [including spleen], and gastrointestinal [including liver], and those associated with clinical signs/symptoms).

[d] All patients must have clinical response assessments (including targeted physical examination and laboratory examinations) at interim response assessment (within 14 days of Cycle 4 Day 1), and 4 weeks after Day 1 of the last cycle. All patients must have a baseline CT scan (or MRI if CT is contraindicated) of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. A follow-up scan must also be performed at the interim response assessment (within 14 days of Cycle 4 Day 1) visit and for final response assessment following completion of combination therapy or early termination (2–3 months after Day 1 of the last treatment cycle). Targeted physical examination and laboratory examinations should be repeated to confirm that patients are still in response prior to confirmatory CT or MRI scan. Imaging evaluations at subsequent study visits are only required to confirm a new response. Imaging evaluations must be performed within 2 weeks for patients who meet the clinical criteria for PD (i.e., increased or de novo enlargement of liver, spleen, or lymph nodes on physical examination) in the absence of laboratory or histopathologic criteria for PD. MRI scans of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used instead of CT scans in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis. If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study.

[e] A bone marrow examination must be performed at screening. For those patients who have achieved a CR or cytopenic CR (including a CT scan indicating a poss ble CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR at least 8 weeks following the initial clinical assessment of CR. A bone marrow aspirate should be obtained for MRD assessment to confirm a molecular CR. Bone marrow examination should be performed as needed within 2 weeks for patients who show clinical suspicion for PD (i.e., increased or de novo enlargement of liver, spleen, or lymph nodes on physical examination) in the absence of laboratory or histopathologic criteria for PD. Any additional/unscheduled bone marrow examinations performed during the study will be at the discretion of the investigator.

[f] Required for all women of reproductive potential (see inclusion criteria).

[g] HBsAg, IgG anti-HBcAb, and Hep C Ab serology (also HCV, and RNA by polymerase chain reaction if the patient is HCV antibody positive) required.

[h] For hepatitis B core antibody–positive patients, the HBV DNA titer needs to be determined using real-time PCR monthly until at least 12 months after the last rituximab dose. Note that during the follow-up period, HBV DNA titer should be performed monthly and the results reviewed by the investigator or designee. The patient does not need to have any other procedures besides this laboratory test between the 12-week follow-up visits unless clinically indicated.

[i] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count), platelet count, absolute neutrophil count, absolute lymphocyte count, and percent or absolute differential counts (e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells).

[j] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen or urea (when BUN not available), creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, a bumin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, and uric acid.

Appendix 1
Schedule of Assessments (cont.)

[k] Peripheral blood lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16, and CD56) measured by flow cytometry are required at baseline, interim response assessment (within 14 days of Cycle 4 Day 1), early termination or end of treatment, 12 weeks after Day 1 of the last cycle of combination therapy, and every 12 weeks thereafter.

[l] Consists of specific gravity, pH, blood, protein, glucose, ketones, and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[m] Patients will have the following samples drawn at screening: serum for β2-microglobulin, whole blood for IgV_H mutational status, p53 and other prognostic mutations, and interphase FISH for chromosomal abnormalities including 17p-, 11q-, 13q-, and trisomy +12. Sample will be taken for both local and central testing of 17p deletion by FISH. In the event a local 17p FISH test is not available, the central test results may be used for randomization.

[n] MRD samples collected at baseline, within 14 days of C4D1 (interim response assessment), completion of Combination Therapy/Early Treatment Termination Visit (if applicable), End of Combination Treatment Response Visit, and 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 months after completion of combination therapy, or any time a patient has a response (PR or CR status), will be measured at a central laboratory.

[o] Predictive biomarker sample will be used for assessment of Bcl-2 family and other relevant markers by RNA and flow in the blood and bone marrow. Whole blood predictive biomarker sample is required for all patients at screening and at time of progression (early termination if applicable) or at end of treatment, one tube each for protein and RNA analysis of Bcl-2 family members. A predictive bone marrow aspirate sample (1 mL each for protein and RNA analysis) should be drawn for all patients at screening. Aspirate samples should be split from samples obtained for International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute Working Group or International Working Group criteria assessment whenever poss ble. If aspirate sample is limiting then protein should be prioritized over RNA sample. Please note that a bone marrow biopsy and aspirate is not required at the time of progression (unless it is needed to confirm or rule out PD); however, if it is performed then a predictive bone marrow biomarker sample should also be drawn. A sample for Bcl-2:Bim complex by protein in blood will be collected for Arm B patients before dosing on Cycle 1 Day 1.

[p] If formalin fixed specimen of bone marrow biopsy is collected at screening by the site per standard clinical assessment of the patient, a sample should be provided for IHC analysis of Bcl-2 family.

[q] Residual tumor specimens are requested at screening and optional blood samples are requested at C1D1 and at the end of combination therapy visit or End of Combination Treatment/Early Treatment Termination Visit for collection and storage at the Roche Clinical Repository.

[r] Rituximab will be administered at 375 mg/m^2 IV on Day 1 of Cycle 1 followed by 500 mg/m^2 IV on Day 1 of Cycles 2 through 6. Investigators will have the option of administering the rituximab dose for Day 1 of Cycle 1 over 2 days (e.g., 100 mg IV on Day 1 of Cycle 1 followed by the remainder of the 375 mg/m^2 dose on Day 2 of Cycle 1).

[s] Bendamustine will be administered at 70 mg/m^2 IV on Days 1 and 2 of Cycles 1 through 6.

[t] The MDASI questionnaire will be completed at home on the specified days. An interactive voice response solution (IVRx) will be used to capture MDASI questionnaire data.

[u] Patients should complete the questionnaires prior to study drug administration and any other study assessments. PRO assessments should be performed prior to progression, at the time of progression, and at the first assessment after progression.

[x] An ECG is required at screening only and as clinically indicated for subsequent visits.

[y] A bone marrow aspirate should be obtained for MRD assessment in the bone marrow in all responders (CR+PR) at the End of Combination Treatment Response Visit or any time after, if the patient becomes a responder. A sample of the bone marrow examination performed at Screening will also be used to assess MRD in the bone marrow.

[z] Assessment is required but may not be applicable.

Appendix 2
Schedule of Pharmacokinetic Assessments

Patients Randomized to Arm A (Venetoclax + R)

Blood samples to assess venetoclax concentrations will be collected at the following timepoints:

Visit	Timepoint	Sample Type
Cycle 1 Day 1	Pre-venetoclax dose 4 h (± 1 h) post-venetoclax dose	Plasma
Cycle 4 Day 1	Pre-venetoclax dose 4 h (± 1 h) post-venetoclax dose	Plasma

h = hour.

Note: An unscheduled PK sample will be collected if TLS is observed. An unscheduled PK sample will be collected in case of early termination.

Appendix 3
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

EORTC QLQ-C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Patient's identification number: _____
Patient's date of birth (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself, or using the toilet?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4

Appendix 3
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

Appendix 3
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Appendix 4
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-CLL16)

EORTC QLQ-CLL16
QOL.QLFORM='EORTC QLQ-CLL16'

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you lost weight?	1	2	3	4
32. Have you had a dry mouth?	1	2	3	4
33. Did you bruise?	1	2	3	4
34. Did you have abdominal discomfort?	1	2	3	4
35. Has your temperature been going up and down?	1	2	3	4
36. Did you have night sweats?	1	2	3	4
37. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
38. Did you feel ill or unwell?	1	2	3	4
39. Did you feel lethargic?	1	2	3	4
40. Have you felt "slowed down"?	1	2	3	4
41. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
43. Have you had trouble with chest infections?	1	2	3	4
44. Have you had trouble with other infections?	1	2	3	4
45. Have you needed repeated courses of antibiotics?	1	2	3	4
46. Have you worried about picking up an infection?	1	2	3	4

Appendix 5
M.D. Anderson Symptom Inventory (MDASI) Questionnaire

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

M. D. Anderson Symptom Inventory (MDASI – CLL - AMGEN)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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Page 1 of 2

MDASI-Core - English

Appendix 5
M.D. Anderson Symptom Inventory (MDASI) Questionnaire (cont.)

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
14. Your night sweats at their WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Fevers and chills at their WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Lymph node swelling at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your diarrhea at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your bruising easily or bleeding at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your constipation at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	DID NOT INTERFERE 0	1	2	3	4	5	6	7	8	9	INTERFERED COMPLETELY 10
20. General activity?	○	○	○	○	○	○	○	○	○	○	○
21. Mood?	○	○	○	○	○	○	○	○	○	○	○
22. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
23. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
24. Walking?	○	○	○	○	○	○	○	○	○	○	○
25. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

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Page 2 of 2

MDASI-Core - English

DRAFT

Appendix 6
EQ-5D (U.S. Version)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

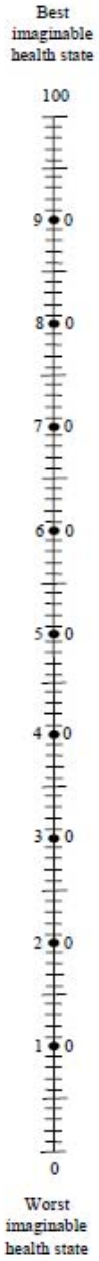
2

Appendix 6
EQ-5D (U.S. Version) (cont.)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

Appendix 7
ECOG Performance Status Scale

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

Appendix 8
Treatment Options for CLL (Adapted from NCCN Version 4.2014 and 2011 ESMO Clinical Practice Guidelines)

CLL Treatment Options per NCCN Guidelines (v 4.2014)

Treatment Options for Patients WITHOUT the 17p deletion		
Front-line		
Frail patients with significant comorbidities	Age ≥ 70 or younger with significant comorbidities	Age < 70 or older patients without significant comorbidities

• Chlorambucil + GA101
• Chlorambucil ± rituximab
• Single agent rituximab
• Pulsed corticosteroids
• Chlorambucil
	• Chlorambucil + Obinutuzumab
	• Chlorambucil ± rituximab
	• Bendamustine ± rituximab
	• Cyclophosphamide, prednisone ± rituximab
	• Single agent rituximab
	• Fludarabine ± rituximab
	• Cladribine
	• Chlorambucil
		• Chemoimmunotherapy
		  ○ FCR
		  ○ FR
		  ○ PCR
		  ○ B ± R
		  ○ Chlorambucil + Obinutuzumab

Relapsed/Refractory Disease		
Long duration of response (18-36 months)	Short response and age ≥ 70	Short response for age < 70 or older patients without significant comorbidities
• Retreat with first line therapy	• Ibrutinib • Idelalisib + rituximab • Reduced dose FCR or PCR • B ± R • HDMP + rituximab • Chlorambucil ± rituximab • Ofatumumab • Alemtuzumab ± rituximab • Lenalidomide ± rituximab • Dose dense rituximab (cat 2B)	• Ibrutinib • Idelalisib + rituximab • Chemoimmunotherapy (e.g., FCR, PCR, BR, fludarabine + alemtuzumab, RCHOP, OFAR • Ofatumumab • Lenalidomide ± rituximab • Alemtuzumab ± rituximab • HDMP + rituximab

Appendix 8
Treatment Options for CLL (Adapted from NCCN Version *4*.2014 and 2011 ESMO Clinical Practice Guidelines) (cont.)

CLL Treatment Options per NCCN Guidelines (v 4.2014) (cont.)

Treatment Options for Patients WITH the 17p deletion
Front-line
• FCR • FR • HDMP + rituximab* • Alemtuzumab ± rituximab • Obinutuzumab + chlorambucil • Ibrutinib
Relapsed/Refractory Disease
• Alemtuzumab ± rituximab • RCHOP • CFAR • HDMP ± rituximab • Ibrutinib • Idelalisib + rituximab • Lenalidomide ± rituximab • Ofatumumab • OFAR

* For the purpose of this trial, HDMP + rituximab cannot be the only previous line of therapy.

Appendix 8
Treatment Options for CLL (Adapted from NCCN Version *4*.2014 and 2011 ESMO Clinical Practice Guidelines) (cont.)

CLL Treatment Options per ESMO Guidelines (adapted from Eichhorst et al. 2011)

Treatment Options for Patients WITHOUT the 17p deletion		
Front-line		
Good PS	Poor PS	
• FCR	• Chlorambucil	
Relapsed/Refractory Disease		
Early Relapse (< 12-24 months to relapse after monotherapy or < 24-36 months to relapse after chemoimmunotherapy)		
Good PS after chemoimmunotherapy	Good PS after monotherapy	Poor PS
• Alemtuzumab ± fludarabine or BR followed by ASCT	• FCR	• FCR • bendamustine • alemtuzumab • ofatumumab • HDMP + rituximab
Late Relapse (> 12-24 months after monotherapy or > 24-36 months after chemoimmunotherapy)		
Any PS: repeat first–line therapy		

Treatment Options for Patients WITH the 17p deletion	
Frontline	
Good PS	Poor PS
• FCR or aletuzumab ± fludarabine followed by ASCT	• Alemtuzumab
Relapsed/Refractory Disease	
Good PS	Poor PS
• Alemtuzumab ± fludarabine followed by ASCT	• Alemtuzumab

ASCT = allogeneic stem cell transplantation; BR = bendamustine, rituximab; CFAR = cyclophosphamide, fludarabine, alemtuzumab, rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CLL = chronic lymphocytic leukemia; ESMO = European Society for Medical Oncology; FCR = fludarabine, cyclophosphamide, rituximab; FR = fludarabine, rituximab; HDMP = high-dose methylprednisolone; NCCN = National Comprehensive Cancer Network; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab; PCR = pentostatin, cyclophosphamide, rituximab; PS = Performance Status.

Appendix 9
Sample List of Prohibited and Cautionary Medications

Type	Example Medications
Prohibited during ramp-up period and cautionary at the designated dose (400mg)	
Strong CYP3A inducers	Avasimibe,carbamazepine (Tegretol®), *cyproterone, efavirenz, enzalutamide, etravirine, hyperforin, mitotane, modafinil, nevirapine, oxcarbazepine,* phenobarbital, phenytoin (Dilantin®), rifampin (Rifadin®), and St. John's Wort
Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, and nafcillin,
Strong CYP3A inhibitors [b]	Boceprevir, clarithromycin, *cobicistat*, conivaptan, *danoprevir/ritonavir*, *diltiazem*, *elvitegravir/ritonavir*, *idelalisib*[a], indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, *paritaprevir/ritonavir combinations*, posaconazole, saquinavir, telaprevir, *tipranavir/ritonavir*, telithromycin, and voriconazole
Moderate CYP3A inhibitors [b]	Amprenavir, aprepitant, atazanavir, *cimetidine*, ciprofloxacin, *clotrimazole* crizotinib[a], *cyclosporine*[a], darunavir/ritonavir, *dronedarone,*erythromycin, fluconazole, fosamprenavir, imatinib[a], *isavuconazole, tofisopam* and verapamil
Cautionary throughout the study	
Warfarin	–
Weak CYP3A inducers	Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, and vemurafenib[a]
Weak CYP3A inhibitors	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide[a], *chlorzoxazone,* cilostazol, fluoxetine, *fosaprepitant*, ginkgo, goldenseal, isoniazid, *istradefylline*, *ivacaftor*, *lomitapide*, oral contraceptives, pazopanib[a], ranitidine, ranolazine, *tacrolimus,* ticagrelor, and zileuton
P-gp substrates	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus[a], fexofenadine, lapatinib[a], loperamide, maraviroc, nilotinib[a], ranolazine, saxagliptin, sirolimus[a], sitagliptin, talinolol, tolvaptan, and topotecan[a]
BCRP substrates	Methotrexate[a], mitoxantrone[a], irinotecan[a], lapatinib[a], rosuvastatin, sulfasalazine, topotecan[a]
OATP1B1/1B3 substrates	Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, and olmesartan

Appendix 9
Sample List of *Prohibited* and Cautionary Medications (cont.)

Type	Example Medications
P-gp inhibitors	Amiodarone, azithromycin, captopril, carvedilol, felodipine, quercetin, *quinidine,* ronalzine, and ticagrelor
BCRP inhibitors	Gefitinib [a]
OATP1B1/B3 inhibitors	Gemfibrozil, eltrombopag, , and tipranavir

BCRP=breast cancer resistance protein ; OATP1B1=organic anion transporter protein 1B1; OATP1B3=organic anion transporter protein 1B3; P-gp=P-glycoprotein 1.

Note: This is not an exhaustive list. For an updated list, see the following link: *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm* In addition to the medications listed in this table, patients receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruits.

[a] These are anticancer agents; consult the Medical Monitor before use.

[b] After discontinuation of a strong or moderate CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

COMMONLY USED CYP1A2 INHIBITORS AND INDUCERS (DRUGS, FOODS, OVER-THE-COUNTER MEDICATIONS AND SUPPLEMENTS)

Based on the USPI for bendamustine, no formal clinical assessments of pharmacokinetic drug–drug interactions between bendamustine and other drugs have been conducted. Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites.

The medications listed below are not contraindicated; however, caution should be used or alternative treatments with medications that are not CYP1A2 inhibitors or inducers should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed for your patient's medical condition. This list is not exhaustive.

Appendix 9
Sample List of *Prohibited* and Cautionary Medications (cont.)

CYP1A2 Inhibitors (cautionary)	CYP1A2 Inducers (cautionary)
Amiodarone	Cruciferous vegetables (broccoli, cauliflower, arugula, brussel sprouts, cabbage, kale, chard, turnips, radishes, wasabi, bok choy, watercress, collard greens)
Cimetidine	Char-grilled meat
Ciprofloxacin	Beta-naphthoflavone
Enoxacin,	
Fluoroquinolones	Methylcholanthrene
Fluvoxamine	Modafinil
Furafylline	Nafcillin
Interferon	Omeprazole
Methoxsalen	Smoking/tobacco
Mexiletine	*Phenytoin*
Mibefradil	*Rifampin*
Oral contraceptives	*Ritonavir*
Zafirlukast	*Teriflunomide*

The bendamustine USPI recommends that caution be used or alternative treatments be considered if treatment with one of these listed drugs or substances or another CYP1A2 inhibitor or inducer is needed. Please contact the study principal investigator if you have further questions.

Appendix 10
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia

Please see the "Imaging Site Operations Manual" for details of imaging acquisition and guidance on response assessment.

Based on iwCLL guidelines (Hallek et al. 2008)

SELECTION OF TARGET LESIONS IN IMAGING OR INDICATOR LESIONS IN PE

Up to six of the largest dominant nodes or tumor masses as well as 6 extra-nodal lesions selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions at baseline

  All nodal lesions must measure

  $>$1.5 cm in greatest transverse diameter (GTD) regardless of short axis measurement
- All extranodal lesions must measure $\geq$10 mm in the GTD
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions
- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Measurable extranodal disease should be assessed in a manner similar to that used for nodal disease.

SELECTION OF NON-TARGET LESIONS IN IMAGING OR INDICATOR LESIONS IN PE

All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions. Examples of non-target lesions include:

- Abnromal (according to the same size criteria as target lesion) measurable lesions beyond the maximum number of target)
- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly and hepatomegaly (in CT only)
- Measurable lesions beyond the maximum number of six
- Groups of lesions that are small and numerous

- Pleural/pericardial effusions and/or ascites
- Effusions, ascites or other fluid collections will be followed as non-target lesions.

  Existing effusions/ascites: Effusions, ascites or other fluid collections will be followed as non-target lesions. At each time point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.

  New effusions/ascites: Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions.

Non-target lesions will be qualitatively assessed at each subsequent timepoint to check if they are still abnormal or normalized.

REPORTING CONVENTIONS

UNABLE TO EVALUATE (UE) LESION CATEGORY

This category is reserved for target and non-target lesions that are deemed unevaluable because 1) subsequent (post-baseline) exams had not been performed, 2) lesions could not be evaluated due to poor radiographic technique or poorly defined margins, or 3) lesions identified at baseline were not at a subsequent time point.

Examples of UE lesions are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe, or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples the boundaries of the lesion can be difficult to distinguish. Every effort should be made to assign measurements to lesions that develop less distinct margins because they become much smaller. Another example is the instance when lesions identified at baseline were not imaged at a subsequent time point unless the lesions are not imaged because of complete resolution. Lesions that cannot be measured or evaluated will be classified for that time point as UE.

If a target lesion is classified as UE post-baseline, the SPD/area (whichever applies) of the target lesions cannot accurately be determined for that time point a response of CR, PR, or SD cannot be assigned for that time point and the response assessment will be UE unless unequivocal progression is determined on the basis of non-target or new lesions, or the evaluable target lesions.

PD can be determined without evaluation of all sites of disease based on the GTD, area or SPD for target lesions, evaluation of unequivocal progression in non-target lesions or observation of a new lesion within the available radiographic or clinical assessments.

Appendix 10
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

TOO SMALL TO MEASURE (TSTM) /BELOW MEASURABLE LIMIT (BML) LESION CATEGORY

Any target lesion findings identified on baseline images, which at a subsequent time point decreases in size to <5 mm in any dimension, should be categorized as TSTM. The lesion, node or mass should be assigned measurements of 5 mm $\times$ 5 mm (for the GTD and the short axis) on the Source Document for the purpose of calculating the area. If that lesion increases in size to ≥ 5 mm in any dimension afterwards, its true size (GTD and short axis) should be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

COMPLETE RESPONSE

Complete response (CR) requires all of the following criteria as assessed no earlier than 2 months after completion of therapy:

- 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)
- Blood counts above the following values

  Neutrophils $> 1.5 \times 10^9$/L (1500/μL) (without growth factors)

  Platelets $> 100 \times 10^9$/L (100 000/μL) (without platelet transfusion or growth factors)

  Hemoglobin $>$ 110 g/L (11 g/dL) (without blood transfusions or erythropoietin)
- Bone marrow at least normocellular for age, with $<30\%$ of nucleated cells being lymphocytes. Lymphoid nodules should be absent. Bone-marrow aspirate and biopsy should be performed 3 months after last treatment when clinical and laboratory results listed above demonstrate that a CR/cytopenic CR has been achieved. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. A marrow biopsy should be compared with a pretreatment marrow if available. Patients who are otherwise in a CR, but whose bone marrow nodules can be identified histologically, should be considered to be in partial response (PR [nodal PR]). Immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than or chronic lymphocytic leukemia (CLL) cells.

Appendix 10
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

COMPLETE RESPONSE WITH INCOMPLETE BONE MARROW RECOVERY

For patients who fulfill the criteria for CR (including bone marrow), but who have persistent cytopenia, the marrow evaluation described above should be performed with scrutiny and should not show any clonal infiltrate.

NODULAR PARTIAL RESPONSE (nPR)

In some cases, lymphoid nodules can be found, which often reflect residual disease. These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells.

PARTIAL RESPONSE

To be considered PR, patients must exhibit the following features for at least 2 months. At least two of the following criteria must be met:

- $\geq$ 50% decrease in peripheral blood lymphocyte count from the pretreatment value.
- $\geq$ 50% reduction in lymphadenopathy (sum of longest diameter of the 6 largest lymph nodes by physical examination and 50% reduction in the sum of product of diameter of 6 largest lymph nodes measured by computed tomography [CT] scan). There should be no increase in any node and no new enlarged lymph node. In small lymph nodes ($<$ 2 cm in diameter), an increase of less than 25% is not considered to be significant.
- $\geq$ 50% reduction of liver and/or spleen enlargement if enlarged at baseline as assessed by physical examination.

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

- Neutrophils $>1.5 \times 10^9$/L (1500/μL) (without growth factors) or $\geq$50% of pretreatment value
- Platelets $>100 \times 10^9$/L (100 000/μL) (without platelet transfusion or growth factors) or $\geq$50% of pretreatment value
- Hemoglobin $>$110 g/L (11 g/dL) (without blood transfusions or erythropoietin) or $\geq$ 50% of pretreatment value

Appendix 10
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

PROGRESSIVE DISEASE

Progressive disease (PD) during or after therapy will be characterized by at least one of the following:

- ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5×10^9/L.

  During combination treatment, the increase should be assessed against Cycle 1, Day 1 (precycle) lymphocyte count and not - cycle lymphocyte counts, which may not be stable.

  After treatment, the increase should be assessed against the lowest lymphocyte count assessed at the first follow-up visit after the end of combination treatment.
- Appearance of new palpable lymph nodes (> 15 mm in longest diameter) or any new extra-nodal lesion (regardless of size)
- ≥ 50% increase in the longest diameter of any previous site of lymphadenopathy
- ≥ 50% increase in the enlargement of the liver and/or spleen as determined by measurement below the relevant costal margin or appearance of palpable hepatomegaly or splenomegaly that was not previously present
- Transformation to a more aggressive histology (e.g., Richter syndrome or plasmacytoid lymphocytic lymphoma with > 55% prolymphocytes); whenever possible, this diagnosis to be supported by lymph node biopsy

After treatment, the progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL) or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100,000/μL), that occurs no earlier than 3 months after end of therapy defines progression if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

STABLE DISEASE

Patients who have not achieved a CR or a PR or who have not exhibited PD will be considered to have stable disease.

Appendix 10
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

Table 1 iwCLL 2008 Criteria for Tumor Response

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) at Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Group A				
Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%[c]	Increase 50%[d] or any new LN > 1.5 cm	Change of −49% to +49%[a]
Blood Lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase 50% over baseline (≥ 5000 μL)	Change of −49% to +49%
Hepatomegaly[b]	None	Decrease ≥ 50%	Increase ≥ 50%[c]	Change of −49% to +49%
Splenomegaly[b]	None	Decrease ≥ 50%	Increase ≥ 50%[c]	Change of −49% to +49%
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules; hypocellular marrow defines CRi	N/A	N/A	N/A
Group B				
Platelet Count	> 100,000/μL[d]	> 100,000/μL or increase ≥ 50% from baseline[h]	Decrease of ≥ 50% from baseline secondary to CLL	Change of −49% to +49%
Hemoglobin	> 11.0 g/dL[d]	> 11.0 g/dL or increase ≥ 50% from baseline[h]	Decrease of 2 < g/dL from baseline secondary to CLL	Increase to ≤ 11.0 g/dL over baseline, or decrease < 2g/dL
Neutrophils	> 1500/μL[d]	> 1500/μL or increase ≥ 50% from baseline[h]	Decrease of ≥ 50% from baseline secondary to CLL	N/A

Appendix 10
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

Table 1 iwCLL 2008 Criteria for Tumor Response (cont.)

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) at Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Other Considerations				
New Lesions	None	None	Appearance of new palpable lymph nodes (>1.5 cm in longest diameter) or any new extra nodal lesion (regardless of size) or transformation to a more aggressive histology, e.g. Richter Syndrome[d]	None
Non-Target Lesions	Nodes must be normal size as visually estimated; extra nodal and other assessable disease should be absent	No change/decreased	Unequivocal progression	No change or decrease or non-substantial increase

Appendix 10
Definitions of Response and Progression for Patients with Chronic Lymphocytic Leukemia (cont.)

Table 1 iwCLL 2008 Criteria for Tumor Response (cont.)

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) at Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Target Extra Nodal Disease	Absence of any nodal disease by physical examination (palpable, visualized extra nodal) and CT scan	≥50% decrease in SPD	≥50% increase in the longest diameter of any extra nodal lesion	Not CR, CRi, PR, or SD

CLL = chronic lymphocytic leukemia; LN = lymph nodes; N/A = not applicable; SPD = sum of the products of diameters; CRi = complete remission with incomplete marrow recovery.

[a] CR also requires the lack disease-related constitutional symptoms.

[b] Transformation to a more aggressive histology (e.g., Richter Syndrome) would also qualify as a PD.

[c] Sum of the products of multiple LNs (as evaluated by CT scans). Note in eCRF if by physical examination only.

[d] Increase in SPD of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. Degree of change in LN or lymphocyte counts should be measured from nadir (lowest post-treatment) values.

Appendix 11
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

FIRST DOSE OF VENETOCLAX OR DOSE INCREASE

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not < 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

In addition to the recommendations in the table below, for patients with CLL/SLL receiving first dose of venetoclax:

- For potassium increase $\geq$0.5 mmol/L from baseline, or any value $>$5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow guideline.
- For phosphorus increase of $>$0.5 mg/dL AND $>$4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

Appendix 11
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Table 1 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still <upper limit of normal (ULN), manage per potassium ≥ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium <ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium >upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV×1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If potassium <ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV×1. • Administer insulin 0.1 U/kg IV+D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. ○ If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.

Appendix 11
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Table 1 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from predose level	• Administer rasburicase (dose per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Corrected calcium ≤7.0 mg/dL (1.75 mmol/L) OR Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus >10 mg/dL) • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Appendix 11
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Table 1 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Abnormality	Management Recommendations
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours STAT.

IV = intravenous; ULN = upper limit of normal; WNL = within normal limits.

ONGOING DOSING OF VENETOCLAX

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (e.g., 48 or 72 hours) are as below. Note: If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
  - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.

- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

Appendix 12
National Cancer Institute–Sponsored Working Group Hematologic Adverse Event Grading Scale for Chronic Lymphocytic Leukemia for Patients with Baseline Abnormal Hematologic Laboratories

Decrease in Platelets [a] or Hgb [b] from Pretreatment Value	Grade	ANC/μL [c] (nadir) ($\times 10^9$ cells/L)
No change–10%	0	≥2000 (≥2.00)
11%–24%	1	≥1500 and <2000 (≥1.5 and <2.0)
25%–49%	2	≥1000 and <1500 (≥1.0 and <1.5)
50%–74%	3	≥500 and <1000 (≥0.5 and <1.0)
≥75%	4	<500 (<0.5)

Source: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood 2008;111:5446–56.

ANC = absolute neutrophil count; Hgb = hemoglobin; Grades: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening.

[a] If, at any level of decrease, the platelet count is $<20 \times 10^9$/L (20,000/μL), this will be considered a Grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (e.g., 20×10^9/L [20,000/μL]), was present before treatment, in which case the patient is not evaluable for toxicity with regard to platelets.

[b] Baseline and subsequent Hgb determinations must be performed before any given infusion.

[c] If ANC was $<1 \times 10^9$/L prior to therapy, the patient is not evaluable for toxicity in ANC.

Appendix 13
Adverse Events Commonly Associated with CLL Study Population and/or Progression of CLL

DISEASE-RELATED EVENTS

- Lymphadenopathy
- Splenomegaly
- Hepatomegaly
- Leukemia cutis (macules, papules, plaques, nodules, ulcers, or blisters)
- Lymphocytosis
- Cytopenias (neutropenia, anemia and thrombocytopenia)
- Febrile neutropenia
- Autoimmune hemolytic anemia
- Autoimmune thrombocytopenia
- Hypogammaglobulinemia
- Infections (bacterial, viral, and fungal)
- Second cancers (Kaposi's sarcoma, malignant melanoma, squamous cell skin cancer, basal cell carcinoma, cancers of the larynx, colorectal cancer and cancers of the lung)
- Fatigue
- Weight loss
- Pyrexia
- Bruising
- Minor hemorrhages
- Pain (any type)

POPULATION-RELATED COEXISTING MEDICAL CONDITIONS:

- Hypertension
- Rheumatoid arthritis/osteoarthritis
- Hyperlipidemia
- Peptic ulcer
- Inflammatory bowel disease
- Coronary artery disease
- Peripheral vascular disease
- Cardiomyopathy
- Valvular disease

Appendix 13
Adverse Events Commonly Associated with CLL Study Population and/or Progression of CLL (cont)

- Atrial fibrillation
- Diabetes mellitus
- Chronic obstructive pulmonary disease
- Cerebrovascular accident
- Transient ischemia attack