Official Title:	**A Phase 3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Ibrutinib Compared to Ibrutinib Alone, in Patients with Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL)**
NCT Number:	NCT02301156
Document Date:	SAP Version 2.2: 10 December 2020

Protocol UTX-IB-301 **Phase 3**

A Phase 3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Ibrutinib Compared to Ibrutinib Alone, in Patients with Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL)

Statistical Analysis Plan

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Version 1.0	**September 9, 2014**
Version 2.0	**October 21, 2016**
Version 2.1	**January 27, 2017**
Version 2.2	**December 10, 2020**

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this prospective statistical analysis plan (SAP) and have approved it for use to analyze the UTX-IB-301 study data.

Reviewers:	**Signatures/Date:**
[redacted] / [redacted]	[redacted] 10-DEC-2020
[redacted] / [redacted]	[redacted] 10-DEC-2020

DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.0	September 9, 2014	Final SAP Version 1.0 Protocol
2.0	October 21, 2016	Amended SAP per Version 2.0 Protocol Dated October 21, 2016
2.1	January 27, 2017	Amended SAP per Version 2.2 Protocol Dated January 27, 2017
2.2	December 10, 2020	Clarify analysis methods for efficacy endpoints

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CLL	Chronic Lymphocytic Leukemia
CMH	Cochran–Mantel–Haenszel
CR	complete response
CT	Computerized Axial Tomography
CTCAE	Common Terminology Criteria for Adverse Events
°C	degrees Celsius
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IRC	Independent Review Committee
ITT	intent-to-treat
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
[redacted]	
PR	partial response
PT	MedDRA Preferred Term
SAE	serious adverse event
SOC	MedDRA System Organ Class
TEAE	treatment-emergent adverse event

2 INTRODUCTION

The original statistical analysis plan (SAP) was based on TG Therapeutics Protocol UTX-IB-301, dated September 9, 2014. This SAP, dated December 10, 2020 is based on the revised Protocol UTX-IB-301, dated July 31, 2017. The SAP summarizes key aspects of the study to provide context for statistical methods and presents details of the statistical methods that the sponsor plans to use to address the study aims. The statistical principles applied in the design and planned analyses of this study are consistent with ICH guidelines E9 (Statistical Principles for Clinical Trials).

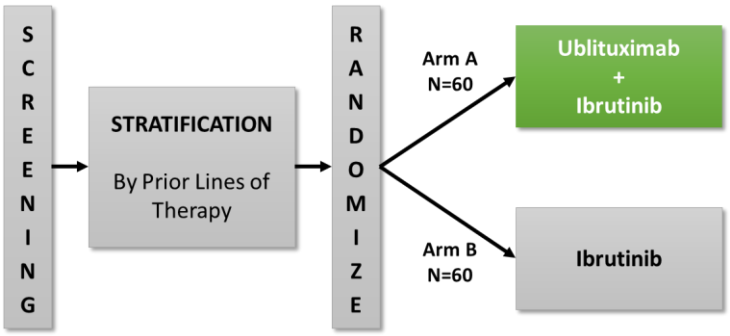
[redacted]

The SAP may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the approved plan will be noted in the clinical study report.

3 STUDY DESCRIPTION

3.1 STUDY DESIGN

This study is a fixed-dose, randomized, two-arm Phase 3 trial to assess the efficacy and safety of ublituximab in combination with ibrutinib compared to ibrutinib alone in patients with CLL who have received at least one prior standard treatment regimen and who have at least one high-risk cytogenetic abnormality (17p deletion, 11q deletion, and/or P53 gene mutation).



Following screening, patients meeting the inclusion/exclusion criteria will be randomized in a 1:1 ratio to one of the following treatment regimens:

- Arm A: Ublituximab + ibrutinib
- Arm B: Ibrutinib

Randomization will be stratified according to prior lines of therapy (1 prior vs. 2 or more prior lines of therapy)

All study patients will be evaluated for response after cycles 2, 4, and 6, then every 3 cycles thereafter if patient is on active treatment, or approximately every 3 months thereafter if patient is in follow up. The best clinical response as well as disease progression will be determined by an Independent Review Committee (IRC).

Patients will continue treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue study treatment for reasons other than disease progression will continue to be followed for progression and/or survival approximately every 3 months.

Upon first assessment scan of the last randomized patient, and site submission of all required efficacy and safety data, the independent DSMB will review the primary and secondary efficacy analyses, and safety data.

3.2 STUDY TREATMENT

Treatment will be administered on an outpatient basis in 4-week (28 day) cycles. Patients randomized to Arm A will receive ublituximab and ibrutinib, while patients randomized to Arm B will receive ibrutinib alone. Treatment cycle of study treatment is summarized in Table 1.

TABLE 1: TREATMENT OVERVIEW BY CYCLE OF STUDY TREATMENT

Cycle 1:

Arm A				Arm B
Ublituximab			**Ibrutinib**	**Ibrutinib**
Day 1	Day 2	Day 8 & 15	Daily	Daily
≤150mg	750 mg	900 mg	420 mg	420 mg

Cycles 2 through 6:

Arm A		Arm B
Ublituximab	**Ibrutinib**	**Ibrutinib**
Day 1 Cycles 2, 3, 4, 5, 6	Daily	Daily
900 mg	420 mg	420 mg

Beyond Cycle 6:

Arm A		Arm B
Ublituximab	**Ibrutinib**	**Ibrutinib**
Day 1 every 3 months thereafter (e.g. cycles 9, 12, etc.)	Daily	Daily
900 mg	420 mg	420 mg

Patients will continue treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons.

3.3 SCHEDULE OF EVENTS

The Schedule of Events is presented in Table 2.

TABLE 2: STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Cycle = 28 days	Screen *	Cycle 1[1]				Cycles 2-6[2]					After Cycle 6[3]	End of study
						C2	C3	C4	C5	C6	q3 Cycles (C9, 12, etc.)	
Procedure\Days	**-21-0**	**D1**	**D2[4]**	**D8**	**D15**	**Day 1**					**Day 1**	
Informed consent	X											
Medical history	X											
Rai Staging	X											
ECOG Performance Status	X	X				X	X	X	X	X	X	X
Physical Examination	X	X				X	X	X	X	X	X	X
Vital signs (pulse, BP, temp)	X	X	X	X	X	X	X	X	X	X	X	X
BM aspirate/biopsy[5]	X											
12-lead EKG	X											
Tumor evaluation[6]	X	After the completion of cycles 2, 4 and 6 then after the completion of every 3 cycles if under treatment or every 3 months if in follow up										
Serology: HCV, HBV, CMV[7]	X											
MRD[8]						For patients in PR or CR at response assessment intervals beginning at the Cycle 6 response assessment						
Hematology[9]	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry[8]	X	X		X	X	X	X	X	X	X	X	X
PT/INR	X					X		X				
Serum Pregnancy Test[10]	X											
Urinalysis	X											
Quantitative Immunoglobulin[11]		X			X		X			X		
β_2-microglobulin	X											
FISH Analysis[12]	X											
[redacted]												
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Evaluation[15]	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Schedule												
Ublituximab Dose		X[16]	X	X	X	X	X	X	X	X	X	

[1] Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have +/- 3 day window
[2] Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have +/- 7 day window
[3] Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have +/- 14 day window
[4] Day 2 visit only required for patients randomized into Arm A.
[5] Unilateral bone marrow aspirate and/or biopsy performed at investigator discretion in patients for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility. In addition, a post-baseline bone marrow biopsy should be completed to confirm potential CR by radiological assessment.
[6] Scans for screening should be completed within 30 days prior to Day 1 of Cycle 1. Response tumor evaluations have a +/- 7 day window. Radiology assessment should include CT or MRI imaging of neck, chest, abdomen, and pelvis.
[7] Serum virology to include HBsAg, HBc antibody and CMV. If HBcAg, HBc antibody, HCV or CMV is positive, patients must be evaluated for the presence of DNA/PCR
[8] Peripheral Blood sample draw (See study manual for all central lab instructions. +/- 7 day window for MRD sample). For patients MRD negative by peripheral blood, a bone marrow sample should be completed to confirm MRD negativity.
[9] Must be obtained prior to ublituximab administration if on a day of infusion.
[10] For women of child bearing potential, completed within 3 days prior to Day 1 of Cycle 1
[11] IgA, IgE, IgG, IgM
[12] For del(13q), del(11q), del(17p), and (12)trisomy, IgHV and P53 gene mutation status in peripheral blood. Central FISH analysis can be performed on UTX-IB-301 study or the TGTX-LAB-001 screening protocol.
[redacted]
[15] If clinically significant adverse event or abnormal result is observed that is not resolved by the end-of treatment visit, continue to monitor and record until stabilization or resolution of event
[16] Patients should receive up to 150 mg on Day 1 and 750 mg on Day 2. Collect a hematology panel prior to Day 2/Cycle 1 infusion.

Ibrutinib Dose		Days 1 – 28 (Daily)	
***Randomize Days -7 to 0**			

3.4 STUDY OBJECTIVES

3.4.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the effect of the addition of ublituximab to ibrutinib on antitumor activity, as measured by the overall response rate (ORR = CR + PR) in patients with previously treated CLL with documented high-risk cytogenetics.

3.4.2 SECONDARY OBJECTIVES

The secondary objectives are to evaluate the effect of the addition of ublituximab to ibrutinib with respect to:

- Complete response (CR) rate
- Duration of response (DOR)
- Time to Treatment Response (TTR)
- Achievement of minimum residual disease (MRD) negativity
- Progression-free Survival (PFS)
- Safety profile

[redacted]

[redacted]

3.5 POWER AND SAMPLE SIZE CONSIDERATIONS

3.5.1 OVERALL RESPONSE RATE

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

The ORR study analysis will be performed when all ITT patients have the opportunity to complete efficacy, safety, and other assessments through at least 16 weeks of evaluation (first planned efficacy evaluation, allowing for a second evaluation to confirm a potential response at first assessment).

3.6 RANDOMIZATION

In this open label study, approximately 120 patients will be centrally randomized in a 1:1 fashion to one of the two treatment regimens. Investigators will use an interactive web response system (IWRS) which will assign patients to either treatment Arm A (ublituximab plus ibrutinib) or treatment Arm B (ibrutinib alone). Randomization will be stratified by prior lines of therapy (1 prior vs. 2 or more prior lines of therapy).

3.7 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population will include all randomized patients. The Treated Population will include all patients who received at least one dose of study medication. The Treated Population will be the same as the Safety Population.

Any ITT patient who meets any of the following criteria below will not be included in the Per Protocol analysis:

- Patients who do not meet the following required eligibility criteria:
    - Diagnosis of CLL which is confirmed as high-risk per the protocol requirement
    - Does not have measurable nodal disease
    - Has been previously treated with ibrutinib or a BTK inhibitor
    - Does not have a baseline or have at least one on-study post baseline efficacy evaluation by the independent radiology committee

4 GENERAL CONVENTIONS

Descriptive and inferential statistics will be used to summarize results of the study. Standard descriptive statistics, such as mean, standard deviation, quartiles, minimum, and maximum, will be calculated for continuous variables. For discrete variables, descriptive analyses will be based on numbers of patients and related percentages.

All tabular presentations will display two columns of results, one for each of the two treatment regimens. Throughout this analysis plan, the phrase "by treatment regimen" will be understood to mean the two groups described in the previous sentence.

In addition to tabular summaries, all relevant eCRF data will be summarized by patient listings.

4.1 DEFINITION OF BASELINE

In general, the last observed measurement prior to or on the first administration of study treatment will be considered the baseline measurement.

4.2 DEFINITION OF TIME

For the purpose of summarizing/analyzing efficacy data, time will be defined relative to the date of randomization. Unless otherwise stated, for visits (or events) that occur on or after the date of randomization, time is calculated as:

- time (days) = visit date (event date) – randomization + 1

For visits (or events) that occur prior to randomization, time is calculated as:

- time (days) = visit date (event date) – randomization date

For listings (such as for adverse events) of the quantity 'days since first/last dose' is defined as:

- days since first/last dose = event date – date of first/last dose

Events that occur on the same day as the first/last dose will therefore be described as occurring zero days from the first/last dose. In most cases, listings will include the number of days since first/last dose of ublituximab/ibrutinib or ibrutinib; however, some listings may present the number of days since first/last dose of study treatment, which is a combination of two agents, or the dose of ibrutinib alone. Labels and footnotes in the data presentations will specify clearly which reference date and therapeutic agent are used.

4.3 MISSING AND PARTIAL DATA

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter and are presented in Appendix A – Imputation Rules for Missing Data.

4.4 SOFTWARE

Unless otherwise stated, all analyses will be conducted using SAS Version 9.2 or higher or other validated software.

4.5 CHANGES TO PLANNED ANALYSES

The Clinical Study Report will document any changes to the SAP made after data base is locked.

5 STUDY POPULATION SUMMARIES

5.1 DISPOSITION

The number and percentage of patients who are included in ITT, Treated Population, Per Protocol populations and the number and percentage of patients withdraw from the study early will be presented by treatment regimen. For randomized patients who withdraw early, the number and percentage withdrawing by withdrawal reason will be presented.

5.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of demographics and baseline characteristics will be presented by treatment arm for the ITT and Treated Population.

The demographic characteristics consist of age, age category (defined below), sex, ethnicity, race, and Eastern Cooperative Oncology Group (ECOG) performance status. Baseline height and weight will also be presented using standard descriptive statistics.

Age (years) will be calculated as (date of informed consent – date of birth) / 365.25.

Age categories, < 65 years and 65 years or older, will be presented using frequencies and percentages.

The number and percentage of patients' ethnicity, race category, cytogenetics category will also be summarized.

5.3 MEDICAL HISTORY

A data listing will present medical history. If useful for interpretation of the results of the study, a table will summarize the data.

5.4 HISTORY OF CHRONIC LYMPHOCYTIC LEUKEMIA

Tables will present information regarding the patients' history of Chronic Lymphocytic Leukemia, including time since initial diagnosis to randomization, primary diagnosis, patient status (relapsed only, or relapsed and refractory), as well as the screening results of the disease assessments and prior lines of therapy.

5.5 PRIOR TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Use of prior treatment for CLL will be presented as frequency counts and percentages.

Prior chemotherapy will be coded using the World Health Organization (WHO) and MedDRA dictionary and summarized by treatment arms for the safety population.

By WHO Drug base substance preferred name using frequency counts and percentages.

By regimen number using frequency counts and percentages on unique combinations of WHO Drug base substance preferred names.

5.6 PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the CRFs will be coded using the WHO or MedDRA dictionary. Prior and concomitant medications will be summarized by treatment arm in the ITT and Treated Population by anatomical therapeutic chemical (ATC) Class Level 4 and WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment component. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment component and no more than 30 days after the last administration of any study treatment component. Medications with start and stop dates that bracket the date of first administration of any study treatment component will be summarized as both prior and concomitant medications.

For the purpose of summarizing prior and concomitant medications, incomplete medication start and stop dates will be imputed as detailed in Appendix A. Based on imputed start and stop dates, medications that clearly stopped prior to date of first administration of any study treatment component will be included in the prior medications table, and medications that clearly started on or after date of first administration of any study treatment component will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables.

5.7 STUDY TREATMENT EXPOSURE

The following will be summarized by treatment arm for each of the two study treatment components using descriptive statistics:

- Number and percentage of patients who received at least one dose (Treated Population analysis)
- Duration of exposure, calculated as (date of last dose – date of first dose + 1) (for subjects who are continuing on treatment at the time of data cutoff, the duration will be data cutoff date – date of first dose +1)
- Number of doses received
- Cumulative dose received

A data listing of reasons for early treatment discontinuation will be summarized (including sites number, patient number, dates of first and last dose administered and last date of contact or visit)

6 EFFICACY ANALYSES

All efficacy analyses will be performed on the ITT population and Treated Population. Measures of tumor response (i.e., ORR, CR rate, DOR, TTR and PFS) will be determined by an Independent Review Committee (IRC).

6.1 PRIMARY EFFICACY OUTCOME

6.1.1 PRIMARY OBJECTIVE: OVERALL RESPONSE RATE

ORR is defined as the proportion of patients with a best overall response of partial response (PR) or complete response (CR). Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the ORR. For the ITT analysis, for each treatment group, the number of patients achieving a response will be divided by the total of patients in the ITT population to yield the proportion responding.

The primary efficacy variable (i.e. ORR) will be analyzed in the ITT population first and then will also be analyzed for the Treated Population.

The ORR will be compared between treatment groups by the CMH Test controlling for the randomization strata. Testing of ORR will be at the 5%, 2-sided statistical significance level.

ORR will also be analyzed based on Per Protocol patients. Additional sensitivity analyses will also be performed as appropriate.

6.1.2 SECONDARY OBJECTIVES

6.1.2.1 COMPLETE RESPONSE RATE

The CR rate is defined as the proportion of patients with a best overall response of complete response (CR). Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the CR rate. For each treatment group, the number of patients achieving a CR will be divided by the total of patients in the Treated Population to yield the proportion responding.

The CR rate will be compared between treatment groups at the 5%, two-sided statistical significance level using the same methodology described in Section 6.1.1.

6.1.2.2 DURATION OF RESPONSE

The Duration of Response (DOR) is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression or death from any cause.

The DOR rate will be compared between treatment groups at the 5%, two-sided statistical significance level using stratified log-rank test. The median DOR will be estimated by Kaplan-Meier method, The hazard ratio (HR) with 2-sided 95% confidence interval will be estimated using stratified Cox regression model. The DOR analysis will be performed for responders only (CR/PR) in the ITT population.

6.1.2.3 TIME TO TREATMENT RESPONSE

The Time to Treatment Response (TTR) is defined as the interval from the date of randomization to the first documentation of CR or PR. In this analysis, subjects who never reached response will be censored at the time of last assessment.

This variable will be analyzed using stratified log-rank test and median TTR will be estimated via Kaplan-Meier methodology. The HR with 95% CI will be analyzed using a stratified Cox regression model.

6.1.2.4 MINIMAL RESIDUAL DISEASE NEGATIVITY RATE

MRD negativity rate is defined as the proportion of patients in the Treated Population who are MRD negative, excluding any patients who remain on study treatment at the time of the analysis and have a Cycle 1/Day 1 start date less than 6 months from the time of the analyses. For the sake of clarity, the MRD negative analysis will exclude those patients that are too early to evaluate because MRD negativity is only tested for patients on study $\geq$ 6 months. Patients who drop off study for any reason prior to their 6 month visit and do not have an MRD assessment will be included in the analysis and considered non-responders.

For each treatment group, the number of patients achieving MRD negativity will be divided by the total number of eligible patients (see above paragraph) to yield the proportion responding. The MRD negativity rate will be compared between treatment groups at the 5%, two-sided statistical significance level using the same methodology described in Section 6.1.1.

6.1.2.5 PROGRESSION-FREE SURVIVAL

Progression-free survival is defined as the time from the date of randomization until the date of first documentation of definitive disease progression or date of death from any cause, whichever occurs first. Patients who die without a reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress or are lost to follow-up will be censored at the day of their last tumor response assessment. If no baseline or post-baseline assessment is available, the patient will be censored at the date of randomization. If death or PD occurs after 2 or more consecutive missing tumor response assessments, censoring will occur at the date of the last response assessment prior to the missed assessments. The use of a new anticancer therapy prior to

the occurrence of PD will result in censoring at the date of last tumor response assessment prior to initiation of new therapy.

This variable will be analyzed using stratified log-rank test, and median PFS will be estimated via Kaplan-Meier methodology. PFS may not be formally analyzed at the time when the planned formal ORR analysis is conducted with approximately 120 patients who have had the opportunity to provide two efficacy assessments as it is expected that the majority of the patients from both treatment arms will not have progressed by the time of the primary ORR analysis (PFS may not be reliably estimated due to high censoring). Following the primary analysis of ORR, PFS may be analyzed at a later date. PFS will be analyzed using a stratified Cox regression model with treatment effect and stratification effect to estimate HR and 95% CI.

Censoring rules for PFS are summarized in Table 3.

TABLE 3: CENSORING RULES FOR PFS

Situation	**Date of Progression or Censor**	**Censored/ Progressed**
No baseline radiological tumor assessments	Randomization date	Censored
No post-baseline tumor assessments and no death reported before data cut-off	Randomization date	Censored
Disease progression	Date of progression	Progressed
No disease progression	Date of last tumor assessment	Censored
Treatment discontinuation for toxicity or other reasons with no disease progression per IRC	Date of last tumor assessment	Censored
Patient lost to follow-up without disease progression	Date of last tumor assessment	Censored
Death before first tumor assessment	Date of death	Progressed
Death between adequate tumor assessments	Date of death	Progressed
Death or disease progression after ≥ 2 missed tumor assessments	Date of last tumor assessment before missed assessments or randomization date if no other tumor assessment in between	Censored
Withdrawal due to symptomatic deterioration without further tumor assessments	Date of last tumor assessment before discontinuation	Censored
Patient use of any anti-cancer therapy and/or surgery for curative intent.	Date of last tumor assessment prior to therapy or surgery, whichever occurs first	Censored
Note: Progression-free survival = date of event / censor – randomization date + 1		

Once the progression and survival dates are derived, PFS will be calculated as follows for patients with a PFS event:

PFS (days) = date of PD or death due to any case – randomization date + 1

(with censoring indicator = event)

For those patients who are censored for a PFS event:

PFS (days) = date of censoring – randomization date + 1

(with censoring indicator = censored)

6.2 ANALYSIS METHODS: DOR AND PFS

The date of definitive progression will be the timepoint at which progression is first identified and confirmed by the independent radiographic committee. Death following the discontinuation of study drug will be considered as an event for the DOR and PFS calculation. Data will be censored on the date of the last tumor assessment (including assessments with a Not Evaluable (NE) outcome) for patients who:

- Start alternative anti-tumor therapy prior to disease progression
- Do not have disease progression within 30 days after discontinuation of study drug(s)

[redacted]

6.5 MULTIPLICITY

6.5.1 PRIMARY OBJECTIVE: OVERALL RESPONSE RATE

If the primary efficacy analysis of ORR is statistically significant for the ITT population, the following secondary outcomes will be tested:

- Complete response rate
- Duration of response
- Time to response

For each of these outcomes, ublituximab + ibrutinib will be compared to ibrutinib. The Hochberg approach will be used to control the type I error rate. The null hypotheses state that the secondary outcomes do not differ between ublituximab + ibrutinib and ibrutinib. The three p-values associated with these three secondary outcomes are denoted p_1, p_2, and p_3. The ordered p-values, from largest to smallest, are denoted $p_{(1)} \geq p_{(2)} \geq p_{(3)}$. Specifically:

- If $p_{(1)}$ is less than 0.05, all three null hypotheses will be rejected.
- Otherwise, if $p_{(2)}$ is less than 0.025, the null hypotheses associated with $p_{(2)}$ and $p_{(3)}$ will be rejected.
- Otherwise, if $p_{(3)}$ is less than 0.0167, the null hypothesis associated with $p_{(3)}$ will be rejected.

If the primary efficacy analysis of ORR is not statistically significant, the secondary efficacy variable defined above will not be formally conducted.

7 SAFETY ANALYSES

Safety analyses will be performed on the Treated Population. Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented by study drug actually received.

Because there is no pre-specified safety outcome defined in terms of AEs, clinically relevant laboratory parameters, or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be post-hoc.

8 ADVERSE EVENTS

Each AE and SAE term recorded on the case report forms (CRFs) will be mapped to a preferred term (PT) using the MedDRA dictionary. The investigator will classify the severity of AEs and SAEs using the NCI CTCAE v4.0 and will assess the relationship of each event to study treatment.

All AEs and SAEs occurring on study will be listed by treatment drug, center, and patient. The frequency and percentages of patients with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and PT, where treatment-emergent is defined as any AE that;

- occurs on or after Cycle 1/Day 1 and through the end of the study or, if serious, up through 30 days after the last dose of study treatment;
- is present before Cycle 1/Day 1 but worsens in intensity or the investigator subsequently considers treatment-related.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A – Imputation Rules for Missing Data. Summaries will display incidence by study drug received and total incidence, and PTs within each SOC will appear in decreasing order of total incidence as well as in alphabetical order. At each level of summarization, a patient will be counted only once for each AE, SOC, or PT experienced within that level.

Related TEAEs, serious TEAEs, Grade 3 or higher TEAEs, related serious TEAEs, related Grade 3 or higher TEAEs, and TEAEs resulting in discontinuation of study treatment will be similarly summarized. Summaries of TEAEs by relationship to the study treatment will also be prepared.

At each level of summarization, a patient will be counted only once for each AE, SOC, or PT experienced within that level. In the summation for AE severity, within each level of AE, SOC, or PT experienced, the one with the highest severity will be included. In the summation for AE's relationship to the study drug, within each level of AE, SOC, or PT experienced, the one with the closest relationship to the study drug will be included.

AEs will be summarized for the treatment that the patient last receives prior to the occurrence of the AEs.

8.1 LABORATORY ASSESSMENTS

Laboratory data for hematology and serum chemistry tests will be reported in International Units. Individual values outside the central laboratory reference ranges will be identified (by "H" for high and "L" for low) in the data listings displaying the absolute values for each patient.

8.1.1 VARIABLES

8.1.1.1 LOCAL LABORATORY ANALYSES

The following laboratory evaluations will be performed at a laboratory affiliated with the site:

- Hematologic profile will be performed at baseline and on Days 1, 2 (Arm A only for ublituximab), 8 & 15 of Cycle 1, Day 1 of Cycles 2-6, and every 3 cycles thereafter.

Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	
Erythrocyte count	Monocytes	
Absolute neutrophil count	Eosinophils	
Absolute leukocyte count	Basophils	

- Serum chemistry will be obtained at baseline and on Days 1, 8 & 15 of Cycle 1, Day 1 of Cycles 2-6, and every 3 cycles thereafter

Serum Chemistry		
Albumin	Creatinine	SGOT [AST]
Alkaline phosphatase	Glucose	SGPT [ALT]
Bicarbonate	LDH	Sodium
BUN	Magnesium	Total bilirubin
Calcium	Phosphorus	Total Protein
Chloride	Potassium	Uric acid

- Serum β-HCG test will be obtained within 3 days prior to the initiation of therapy for women of childbearing potential.
- Coagulation lab tests to include, PT, aPTT, and INR will be drawn at screening.
- Quantitative immunoglobulin (IgG, IgM, IgA, IgE) test will be obtained at pre-dose on Day 1 and Day 15 of Cycle 1, on Day 1 of Cycle 3 and Cycle 6.
- Urinalysis to be obtained at screening (dipstick for pH, protein, glucose, blood, nitrite, leukocytes.
- Beta2-microglobulin to be obtained at screening.
- Serum Virology at screening to include HBsAG, HBc antibody, HCV antibody, and CMV

8.1.1.2 CENTRAL LABORATORY ANALYSES

The following laboratory evaluations will be performed at a central laboratory contracted by the Sponsor:

- FISH analyses at screening for del(13q), del(11q), del(17p), and (12)trisomy, t(11:14), IgHV and p53 mutation
- Minimal Residual Disease negativity analyses in patients with documented PR or CR at response assessment intervals beginning at the Cycle 6 response assessment.

8.1.2 STATISTICAL ANALYSIS

Continuous laboratory test results will be summarized descriptively by study drug received for actual values and for changes from Cycle 1 Day 1. Visits to be summarized include all scheduled post-Cycle 1 Day 1 visits.

Shift from baseline tables for laboratory parameters will be presented. Categories will be based on CTCAE grade (where applicable) or by high/low flags (where CTCAE grades are not defined). Data will be analyzed at all post-Cycle 1 Day 1 visits, by worst grade post-Cycle 1 Day 1. Laboratory tests that have high and low abnormalities will be summarized separately for each direction (e.g., hypocalcemia and hypercalcemia).

Abnormalities in laboratory tests that the investigator considers clinically significant will be recorded and summarized as AEs.

8.2 VITAL SIGNS

8.2.1 VARIABLES

The following vital signs will be summarized:

- Blood pressure (systolic and diastolic, mmHg)
- Oral temperature (Celsius)
- Pulse rate (beats/min)
- Respiration rate (breaths/min)
- Body weight (kg)

8.2.2 STATISTICAL ANALYSIS

Summary tables of vital signs and change from baseline will be presented for all scheduled visits where vital signs were assessed. All recorded vital sign data will be listed.

8.2.3 PHYSICAL EXAM

Physical examination data will be presented in a data listing.

8.2.4 ECOG PERFORMANCE STATUS

ECOG Performance Status will be summarized as shift from baseline tables by visit using frequencies and percentages at all scheduled visits where performance status was assessed.

9 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Major protocol deviations from entry criteria and treatment compliance will be summarized as far as they can be extracted from numeric or coded study data.

10 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

11 REFERENCES

Hallek M., Cheson B.D., Catovsky D., Caligaris-Cappio F., Dighiero G., Dohner H., . . . Kipps R.J. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Wrokshop on Chronic Lymphocytic Leukemia updating the National Cancer Institue - Working Group 1996 Guidelines. *blood, 12*(111), 5446-5456.

12 APPENDIX A – IMPUTATION RULES FOR MISSING DATA

Terminology in this appendix: first dose = first administration of any study treatment

The date of event (death/progression) is the documented date of event.

The missing date will be handled as follows:

What is missing in event date	Imputed value is
Year	
• If month is missing or cannot be confirmed to be earlier than the month of last assessment	the year of last assessment
• If, without considering year, the date of the event is confirmed to be earlier than the date of the last assessment (e.g., January vs November or May 15 vs May 1)	the year of last assessment+1
Month	
• If year of the event is missing or is confirmed to be the same as the year of the last assessment	Month of the last assessment unless the day of death is earlier than the day of the last assessment (5th vs. 10th). In this case the month will be imputed as the month after the month of the last assessment
• If year of the event is confirmed to be after the year of the last assessment	January
Day	1, unless the resulting imputed date is earlier than the last assessment date. In this case the imputed day is the day of the last assessment

Adverse Event

- If onset date is completely missing, onset date is set to date of first dose.
- If (year is present and month and day are missing) or (year and day are present and month is missing):
  - If year = year of first dose, then set month and day to month and day of first dose.
  - If year < year of first dose, then set month and day to December 31st.
  - If year > year of first dose, then set month and day to January 1st.
- If month and year are present and day is missing:
  - If year=year of first dose and
    - ❖ if month = month of first dose then set day to day of first dose date.
    - ❖ if month < month of first dose then set day to last day of month.
    - ❖ if month > month of first dose then set day to 1st day of month.
  - if year < year of first dose then set day to last day of month.
  - if year > year of first dose then set day to 1st day of month.
- For all other cases, set onset date to date of first dose.

Concomitant Medications/Medical History

- If start date is completely missing, start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
- If year and month are present and day is missing, set day to 1st day of month.
- If end date is completely missing, end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31.
- If year and month are present and day is missing, set day to last day of the month.