Official Title: A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with TGR-1202 Compared to Obinutuzumab in Combination with Chlorambucil in Patients with Chronic Lymphocytic Leukemia (CLL)

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Protocol UTX-TGR-304 **Phase 3**

A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with TGR-1202 Compared to Obinutuzumab in Combination with Chlorambucil in Patients with Chronic Lymphocytic Leukemia (CLL)

Statistical Analysis Plan

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Version Final 2.0 March 15, 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-TGR-304 study data.

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1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.00	September 14, 2015	Final Draft
1.1	February 13, 2019	Phrasing around sample size and PFS powering was updated to reflect new language in Protocol UTX-TGR-304 V5.0. Note, this is not a change to the PFS analysis plan and is for clarification purposes only. Powering assumption clarifications have been added for the previously specified ORR analysis. Note, this is not a change to the ORR analysis plan but provides statistical assumptions for purposes of clarification only.
2.0	March 15, 2020	Sections 6.4 and 6.5 describing software to be used and convention for document numbering were removed for administrative purposes. In Section 9.1.1 and throughout, the phrase "tumor assessment" was changed to "disease assessment" to better reflect accepted terminology regarding the assessment of chronic lymphocytic leukemia which is a cancer of the blood. Response categories of CRi (complete response with incomplete marrow recovery) and nPR (nodular partial response) have been added throughout, consistent with the protocol specified response criteria. Clarification was made to specify that the primary and secondary efficacy analyses would occur in the ITT population. Section 9.3.2 regarding MRD negativity rate was modified to remove reference to "MRD positivity at baseline" since no baseline MRD samples are to be obtained in the study. MRD was clarified as being assessed amongst responders only. Section 9.3.3 was added to specify Duration of Response as a secondary endpoint. Section 9.5 Multiplicity was modified for clarity and to reflect the addition of the interim efficacy PFS analysis at a 210 events. Figure 1 was added to depict the testing schema, alpha allocation, and the order of sequential testing of secondary endpoints. Section 9.6 was modified. The interim futility PFS analysis at 75% of target events (210 events) was removed and an

interim PFS analysis to evaluate the superiority hypothesis for Arm A compared to Arm B was added.

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CLL	Chronic Lymphocytic Leukemia
CR	complete response
CRi	Complete response with incomplete marrow recovery
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
nPR	Nodular Partial Response
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	MedDRA Preferred Term
SAE	serious adverse event
SOC	MedDRA System Organ Class
TEAE	treatment-emergent adverse event

3.0 INTRODUCTION

The statistical analysis plan (SAP) is based on:

- Protocol UTX-TGR-304, version 6.0 for FDA's Special Protocol Assessment, dated March 15, 2020,
- FDA Guidance On Cancer Trial Endpoints (Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics),
- FDA guidance on the co-development of two or more new investigational drugs used in combination (Guidance for Industry Co-development of Two or More New Investigational Drugs for Use in Combination)
- ICH guidelines E9 (Statistical Principles for Clinical Trials).

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled, and how censoring procedures will be applied to time to event related variables as well as details on statistical methods to be used to analyze the safety and efficacy data from the study.

[redacted]

An Independent Data Safety Monitoring Board (DSMB) will be established to monitor clinical data on a regular basis during the study. The DSMB may recommend modifications to the study conduct to the Sponsor as specified in the DSMB charter.

An Independent Review Committee (IRC) will be established to provide a blinded review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in disease status and to confirm or refute the determination of the Principal Investigator at the site. CLL response and progression data collected from this study will be subjected to review by the IRC which will be blinded to treatment arm assignment. The review of radiographic and clinical data by the IRC will be performed on an ongoing basis. The specifics of the IRC's processes and reading methods will be described in an Independent Review Charter developed by the contracted imaging facility in conjunction with the Sponsor. The findings of the IRC will be considered primary for analyses of PFS and other efficacy endpoints.

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 the database is locked. Deviations from the approved plan will be noted in the clinical study report.

4.0 STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

PRIMARY OBJECTIVES

- To establish that the combination of ublituximab + TGR-1202 is superior to the combination of obinutuzumab + chlorambucil as measured by Progression-Free Survival (PFS) in patients with CLL

KEY SECONDARY OBJECTIVES

- To establish that the combination of ublituximab + TGR-1202 provides clinical benefit over both ublituximab alone and TGR-1202 alone
- To evaluate and compare the combination of ublituximab + TGR-1202 to the combination of obinutuzumab + chlorambucil with respect to overall response rate in patients with CLL

OTHER SECONDARY OBJECTIVES

- To assess safety, tolerability and other efficacy outcomes.

[redacted]

4.2 STUDY TREATMENT

Investigators will use an interactive web response system (IWRS) to assign patients to one of four treatment arms as follows:

- Arm A: Ublituximab + TGR-1202
- Arm B: Obinutuzumab + Chlorambucil
- Arm C: Ublituximab
- Arm D: TGR-1202

Treatment will be administered on an outpatient basis in 4-week (28 days) cycles, according to the treatment arms below:

Treatment Schema Overview

ARM A: Ublituximab + TGR-1202

Cycle 1:

Ublituximab			TGR-1202
Day 1	**Day 2**	**Day 8 & 15**	**Daily**
150 mg	750 mg	900 mg	800 mg

Cycles 2 through 6:

Ublituximab	TGR-1202
Day 1	**Daily**
900 mg	800 mg

After Cycle 6:

Ublituximab	TGR-1202
Day 1, Q3 months	**Daily**
900 mg	800 mg

ARM B: Obinutuzumab + Chlorambucil

Cycle 1:

Obinutuzumab			Chlorambucil
Day 1	**Day 2**	**Day 8 & 15**	**Day 1 & 15**
100 mg	900 mg	1000 mg	0.5 mg/kg

Cycles 2 through 6:

Obinutuzumab	Chlorambucil
Day 1	**Day 1 & 15**
1000 mg	0.5 mg/kg

After Cycle 6:

No Further Treatment

ARM C: Ublituximab

Cycle 1:

- 150 mg Ublituximab on Day 1
- 750 mg Ublituximab on Day 2
- 900 mg Ublituximab on Days 8 & 15

Cycles 2 through 6:

- 900 mg Ublituximab on Day 1

After Cycle 6:

- 900 mg Ublituximab on Day 1, every 3 cycles (i.e. Cycle 9, 12, 15, etc.)

ARM D: TGR-1202

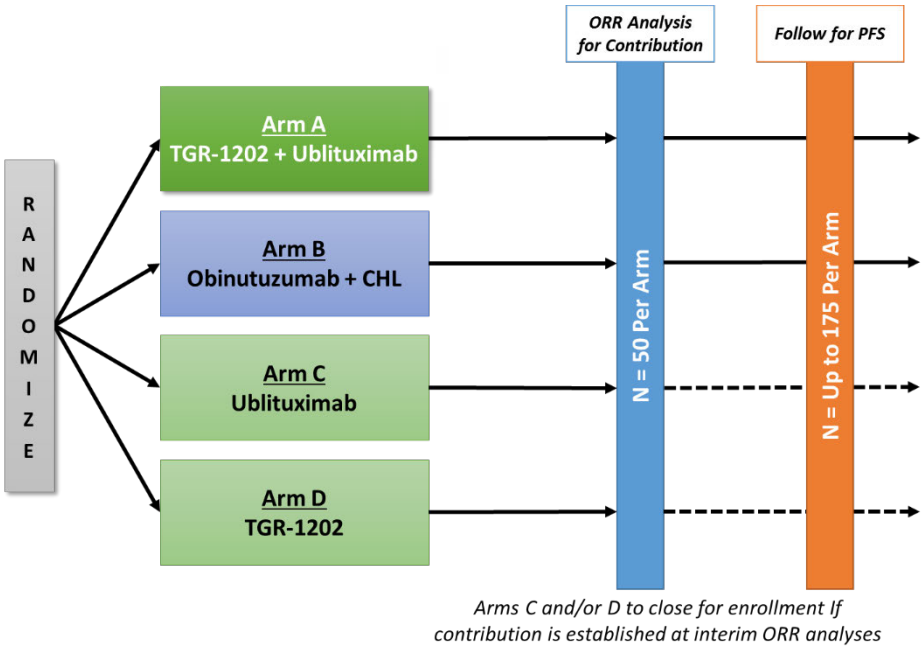
Cycle 1, and Onward:

- 800 mg TGR-1202 once daily until removal from study

Additional information, including premedication procedures can be found in Section 8 of the protocol.

4.3 STUDY DESIGN

This study is designed as a Phase 3, randomized, four-arm trial to evaluate the efficacy and safety of ublituximab in combination with TGR-1202 compared to that of obinutuzumab in combination with chlorambucil (CHL), and to ublituximab alone and to TGR-1202 alone in patients with CLL. While the primary objective of the study is to demonstrate the superiority of Arm A (Ublituximab + TGR-1202) over Arm B (Obinutuzumab + Chlorambucil) as measured by progression-free survival (PFS) and overall response rate (ORR), an interim analysis of ORR among the first 50 patients enrolled into each arm is planned to assess the contribution of each single agent in the ublituximab + TGR-1202 combination regimen.



Following Screening, qualified patients will be randomized in a 1:1:1:1 ratio to one of the four arms:

- Arm A: Ublituximab + TGR-1202
- Arm B: Obinutuzumab + Chlorambucil
- Arm C: Ublituximab
- Arm D: TGR-1202

Randomization will be stratified according to 17p deletion status (presence vs. absence) and treatment status (treatment naïve vs. previously treated). For purposes of stratification, patients will be considered "previously treated" only if they have previously received at least 2 cycles of one or more prior treatment regimens.

During the study period, response assessments should be obtained every 3 cycles for the first 24 cycles. After Cycle 24, evaluate for response approximately every 6 cycles unless clinically indicated sooner. Subjects followed for PFS off treatment should have response assessments done approximately every 6 months unless clinically indicated sooner. The best clinical response as well as disease progression will be determined by an Independent Review Committee (IRC). Patients will remain on study 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 from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression.

The study will include a non-binding interim analysis for ORR at 50 patients per arm, and an interim analysis for PFS solely for purposes of assessing futility at 50% information time (approximately 140 events). A second interim PFS analysis will be conducted at the later to occur of i) 75% information time (210 events), and ii) December 10, 2019, to evaluate the superiority hypothesis for Arm A compared to Arm B. The study will end either at the second interim PFS analysis or at the final PFS analysis after approximately 280 PFS events are observed between Arms A & B. The interim analyses will be performed by the independent DSMB.

4.4 RANDOMIZATION AND BLINDING

The patient must consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Patients who are eligible and who have signed an informed consent will be randomized in a 1:1:1:1 ratio to one of four treatment arms: ublituximab in combination with TGR-1202 (Arm A), obinutuzumab in combination with chlorambucil (Arm B), ublituximab alone (Arm C), or TGR-1202 alone (Arm D). Randomization will be stratified according to 17p deletion status (presence vs. absence) and treatment status (treatment naïve vs. previously treated). For purposes of stratification, patients will be considered "previously treated" only if they have previously received at least 2 cycles of one or more prior treatment regimens.

Investigators will use an interactive web response system (IWRS) to assign patients to one of four treatment arms as follows:

- Arm A: Ublituximab + TGR-1202
- Arm B: Obinutuzumab + Chlorambucil
- Arm C: Ublituximab
- Arm D: TGR-1202

Patients must begin study treatment within 7 days of randomization. Please see the Study Manual for additional information on randomization.

Upon entering patient information into the IWRS, investigators will receive an enrollment approval and a unique patient identifier that will include the randomization assignment. This confirmation

must be received by the site prior to dispensing study drug to the participant. Further details about the patient registration process using the IWRS system will be outlined in the Study Manual.

As this is an open-label study, to protect data integrity, the following procedures will be implemented to ensure all clinical and statistical decisions are made in a treatment blinded manner. The Sponsor, except for Clinical Operations personnel monitoring the study and the Medical Monitor, will be blinded to treatment assignment and specific dosing data within the four individual treatment arms. In addition, unblinded Clinical Operations personnel will not be involved in any discussions regarding the analysis of data after enrollment of the first patient into the trial or any protocol amendment, except those related to safety.

5.0 ANALYSIS POPULATIONS

5.1 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) population will consist of all randomized patients, regardless of administration of study treatment (ublituximab, TGR-1202, obinutuzumab + chlorambucil, or ublituximab + TGR-1202). Analyses of this population will assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications. Patients who received treatment in the group that is different from what they have been randomized to, will be noted in the CSR. The ITT population is the primary analysis population for efficacy analyses.

5.2 SAFETY POPULATION

The safety population will include all randomized patients who received at least one dose of study treatment (ublituximab, TGR-1202, obinutuzumab + chlorambucil, or ublituximab + TGR-1202). Patients who are included in a treatment group that is different from what they have been randomized to will be noted.

5.3 PER PROTOCOL POPULATION

The per protocol population will include all ITT patients without major protocol violations and who have had at least one post-baseline response assessment. Major protocol violations will be documented prior to database lock. Analyses based on per protocol population may be performed.

6.0 GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed using SAS Version 9.2 or higher and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

Continuous (non-survival related) data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, standard deviation, median, 25th and 75th percentiles, minimum, maximum, and percentages will be presented with one decimal.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals will be constructed using the normal approximation without continuity correction.

Data listings will present all data collected on eCRFs by study drug, center, and patient number.

6.1 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.

6.2 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 randomization, time is calculated as:

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

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

time (days) = visit date (event date) – date of randomization.

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 either study treatment. Labels and footnotes in the data presentations will specify clearly which reference date and therapeutic agent are used.

6.3 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 14.1 Appendix A - Imputation Rules for Missing Dates.

7.0 DESCRIPTION OF THE STUDY POPULATIONS

The paragraphs below specify presentations of data for both the ITT and safety populations. If, however, the two populations are almost the same (i.e., safety population is 95% of the ITT population), then only the ITT tables will be presented. A summary of differences between the two populations will be noted in the CSR.

7.1 DISPOSITION

Patient disposition summaries will be presented by treatment arm and will include the number of patients enrolled, randomized, and the number and percentage of randomized patients in the ITT and safety populations. The summaries will also include the reasons for permanent discontinuation of study treatment and study. Disposition by investigational sites will also be presented.

7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

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, prior therapies, 17p deletion status (present vs. absent), and Immunoglobulin heavy chain variable region (IgHV) Mutation Status (unmutated (or IgHV3-21) vs mutated) will also be summarized.

7.3 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.

7.4 HISTORY OF CHRONIC LYMPHOCYTIC LEUKEMIA

Tables will present information regarding the patients' history of Chronic Lymphocytic Leukemia, including time since initial diagnosis, and if applicable, most recent relapse, to randomization.

8.0 TREATMENTS AND MEDICATIONS

8.1 PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the eCRFs will be coded using the WHO or MedDRA dictionary. Prior and concomitant medications will be summarized by treatment arm in the safety 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.

8.2 STUDY TREATMENT EXPOSURE

Study treatment exposure will be summarized by treatment arm. Study treatment consists of the following four therapeutic agents:

- Obinutuzumab;
- Chlorambucil;
- Ublituximab; and
- TGR-1202.

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

- number and percentage of patients complete each cycle;
- number and percentage of patients who received at least one dose;
- number and percentage of patients who had dose interruptions and frequency of dose interruptions;
- duration of exposure, calculated as (date of last dose – date of first dose + 1);
- number of doses received;
- number of doses reductions (for chlorambucil and TGR-1202 only); and
- cumulative dose received.

9.0 EFFICACY ANALYSES

Many of the efficacy measures will be based on disease assessments. The best clinical response as well as disease progression will be determined by an independent review committee (IRC) which will be blinded to treatment arm assignment. Definitive disease progression will be based on standard criteria (Hallek et al. 2008, see Appendix A in the protocol) occurring for any reason (e.g., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis. Detailed procedures to assess response and progression are discussed in Section 10 in the protocol.

9.1 PRIMARY EFFICACY OUTCOMES

9.1.1 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 disease 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 disease assessments, censoring will occur at the date of the last disease 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 disease assessment prior to initiation of new therapy. Censoring rules for PFS are summarized in TABLE 1.

TABLE 1: CENSORING RULES FOR PFS

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

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 cause – 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)

Hypothesis testing for comparison between the treatment arms will be performed using a stratified (by randomization stratification factors) log rank test via [redacted]

[redacted]

[redacted]

For each treatment arm, the median duration of PFS and the proportion of patients progression-free at 6, 12, and 18 months will be estimated using the Kaplan-Meier method. For each estimate, a 95% confidence interval will be reported.

The primary objective that Treatment A is superior to Treatment B will be tested at an overall two-sided 0.04 level of significance.

9.2 KEY SECONDARY EFFICACY OUTCOMES

9.2.1 OVERALL RESPONSE RATE

ORR will be determined according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (Hallek et al. 2008).

Overall Response Rate (ORR) is defined as percent of patients who achieve complete response (CR), complete response with incomplete marrow recovery (CRi), partial response (PR) or nodular partial response (nPR). The response rate comparison between the two treatment arms will be analyzed via a Cochran-Mantel-Haenzel (CMH) test stratified by the randomization factors. The 95% confidence intervals for the response rates as well as for the differences of the response rate based on normal approximations will be presented. Additional logistic analyses model may be used to assess the impact of demographic and baseline parameters as well as the stratification factors.

The key secondary objective that Treatment A provides additional clinical benefit over treatments C alone and D alone will be tested at a two-sided 0.01 level of significance at the interim based on ORR (when approximately the first 50 patients enrolled into each arm provided ORR assessment).

[redacted]

9.3 OTHER SECONDARY EFFICACY OUTCOMES

9.3.1 COMPLETE RESPONSE RATE

The CR rate is defined as the proportion of patients with a best overall response of complete response (CR) or complete response with incomplete marrow recovery (CRi). Patients who do not have a disease 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 or CRi will be divided by the total of patients randomized to yield the proportion responding.

The CR rate will be analyzed using a Cochran-Mantel-Haenzel (CMH) test stratified by the randomization factors. The 95% confidence intervals for the CR rate and the treatment difference based on normal approximation (Active – Control) will be presented.

9.3.2 MINIMAL RESIDUAL DISEASE NEGATIVITY RATE

The MRD negativity rate is defined as the proportion of patients who achieve MRD negativity post-baseline. MRD is assessed only amongst responders, defined as subjects achieving CR/CRi/PR/nPR. Patients who do not have an MRD assessment post-baseline will be considered non-responders and

will be included in the denominator when calculating MRD negativity rate. For each treatment group, the number of patients achieving MRD negativity will be divided by the total number of patients randomized to yield the proportion responding.

The rate of MRD negativity will be analyzed in the ITT population using a Cochran-Mantel-Haenzel (CMH) test stratified by the randomization factors. The 95% confidence intervals for the rate of MRD negativity and the treatment difference (Active – Control) in rate of MRD negativity will be presented

9.3.3 DURATION OF RESPONSE

Duration of Response (DOR) defined as the interval from the first documentation of CR, CRi, PR, or nPR to the earlier of the first documentation of definitive disease progression or death from any cause. The Kaplan-Meier estimator for DOR will be presented for patients who achieve an objective response in each treatment arm. The same censoring rules will be applied as for PFS.

[redacted]

9.5 MULTIPLICITY

The study has the following three pre-specified primary efficacy evaluations:

1. Assessing whether Treatment A is superior to Treatment B based on PFS;
2. Assessing contributions of individual components in Treatment A established based on PFS;
3. Assessing contributions of individual components in Treatment A established based on ORR;

Contributions of individual components of Treatment A will be established if positivity is established for either #2 or #3, above.

To control for the overall Type I error rate at 0.05, an overall two-sided p-value of 0.01 will be used to evaluate #3, at the interim analysis when the first 50 patients in Treatment Arms A, C, and D have provided adequate ORR data (at least one post-baseline disease assessment). If contributions of individual components in Treatment A based on ORR is established at the interim ORR analysis, a formal test of ORR between Treatment A and Treatment B will be conducted at a two-sided 0.01 level following a positive interim PFS analysis or, if the interim PFS analysis is negative, following

the final PFS analysis. Analysis of CR rate and MRD negativity rate will also be conducted sequentially at the two-sided 0.01 level (See Figure 1).

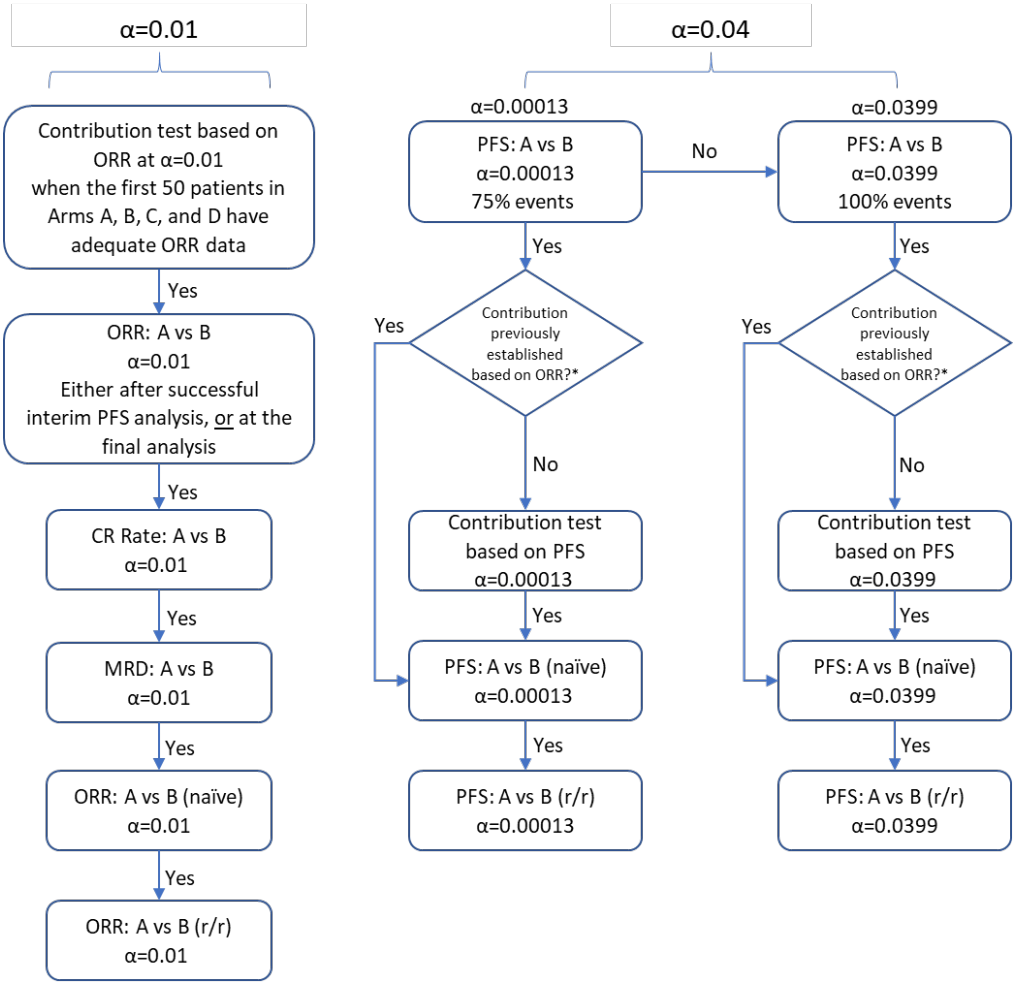
The remaining overall two-sided p-value of 0.04 will be used to evaluate #1 (and to evaluate #2 if #3 is not earlier established to be positive). If #1 is established to be positive and #3 has not been established to be positive at the interim ORR analysis for contribution, the following assessments will be evaluated at the overall two-sided 0.04 significance level to establish #2:

1. Assessing whether treatment A is superior to Treatment C regarding PFS; and
2. Assessing whether treatment A is superior to Treatment D regarding PFS.

[redacted]

Figure 1 below illustrates the testing schema for primary and secondary analyses.

Figure 1. Study UTX-TGR-304 Testing Schema to Control Type I Error for Multiple Analyses



*Contribution test based on ORR is not tested sequentially from PFS, but represents previous testing based on ORR at α=0.01

To control for the overall type I error rate, a claim cannot be made unless all proceeding claims, if any, are made. For completeness, all p-values will be presented.

9.6 INTERIM ANALYSIS

One interim analysis based on ORR will be performed when approximately 50 subjects each in Arms A, B, C and D have provided disease assessments to determine ORR status. If contributions of individual components in Treatment A based on ORR is established at the interim ORR analysis, a secondary claim that Treatment A is superior over Treatment B based on ORR will be tested at a two-side 0.01 level following a positive interim PFS analysis or, if the interim PFS analysis is negative, following the final PFS analysis. Further, should contribution be established at the interim ORR analysis, enrollment into both Arms C and D will be terminated, however enrollment into Arms A and B will continue until 175 patients have been enrolled into each arm. If contribution was unable to be established by ORR at the interim analysis, both single agent arms C and D will be evaluated for PFS.

One interim analysis based on PFS will be performed solely for purposes of assessing futility at approximately 50% information time (140 events). A second interim PFS analysis will be conducted at the later to occur of i) 75% information time (210 events), and ii) December 10, 2019, to evaluate the superiority hypothesis for Arm A compared to Arm B. At this interim analysis, early study termination will be guided by an O'Brien-Fleming monitoring boundary that is preserving the (one-sided) 0.0005 false positive error rate. At 75% of the events (i.e., 210 PFS events), the corresponding Z-value would be 3.81, with corresponding nominal two-sided p=0.00013. If early termination does not occur, nearly all of the two sided 0.04 false positive error rate allocated to PFS would have been preserved, statistical significance for PFS at the 280 event final analysis would be achieved with Z-value 2.06. The study will end either at the second interim PFS analysis or at the final PFS analysis.

An independent DSMB will be established and will conduct all interim analyses in addition to reviewing clinical data periodically throughout the trial. The DSMB may recommend stopping or modifying the trial for safety reasons.

9.7 SAMPLE SIZE

[redacted]

10.0 SUMMARIES OF MEASURES OF SAFETY

Safety analyses will be performed for the safety 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.

10.1 ADVERSE EVENTS

Each AE and SAE term recorded on eCRFs 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 after randomization and through the end of the study or, if serious, up through 30 days after the last dose of study treatment;
- is present before randomization 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. 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.

10.2 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.

10.2.1 VARIABLES

10.2.1.1 LOCAL LABORATORY ANALYSES

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

- Hematologic profile: Hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count. CBC/FBC with differential (3 part differential accepted) and platelet count should be obtained at baseline and on Days 1, 2, 8 & 15 of Cycle 1, Day 1 of Cycles 2 through 6, and every 3 cycles after Cycle 6.
- 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 and INR will be drawn at screening.
- Beta2-microglobulin to be obtained at screening.
- Serum Virology at screening to include HBsAG, HBc antibody, HCV antibody, and CMV
- CLL mutation panel including Fluorescence in situ hybridization (FISH) analyses at screening for del(13q), del(11q), del(17p), and (12)trisomy, t(11:14), IgVH mutation status

10.2.1.2 CENTRAL LABORATORY ANALYSES

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

- Minimal Residual Disease negativity analyses in patients with documented CR

10.2.2 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.

10.3 VITAL SIGNS

10.3.1 VARIABLES

The following vital signs will be summarized:

- Blood pressure (systolic and diastolic, mmHg)
- Pulse rate (beats/min)
- Respiration rate (breaths/min)

10.3.2 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.

10.4 PHYSICAL EXAM

Physical examination data will be presented in a data listing.

10.5 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.

11.0 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.

12.0 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross check of the eCRFs 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.

As this is an open-label study, to protect data integrity, the following procedures will be implemented to ensure all clinical and statistical decisions are made in a treatment blinded manner. The Sponsor, except for Clinical Operations personnel monitoring the study and the Medical Monitor, will be blinded to treatment assignment and specific dosing data within the three individual treatment arms. In addition, unblinded Clinical Operations personnel will not be involved in any discussions regarding the analysis of data after enrollment of the first patient into the trial or any protocol amendment, except those related to safety.

13.0 REFERENCES

Hallek M, et al. (2008). 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: (12):5446-56.

14.0 APPENDICES

14.1 APPENDIX A - IMPUTATION RULES FOR MISSING DATES

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.
    - o if year < year of first dose then set day to last day of month.
    - o 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.