A Phase 2 Study to Assess the Efficacy, Safety, Pharmacokinetic and Pharmacodynamic Parameters of Umbralisib in Treatment Naïve Patients with Chronic Lymphocytic Leukemia (CLL)

NCT04163718

Version 4.0

March 1, 2021

Protocol version/Date: 1.0/ 05 March 2018

2.0/ 27 April 2018

3.0/ 26 November 2018

3.1/ 18 January 2019

3.2/ 28 May 2019

3.3/ 20 Jun 2019
4.0/ 01 March 2021

Local Protocol #: MCC 19585

TITLE: A Phase 2 Study to Assess the Efficacy, Safety, Pharmacokinetic and Pharmacodynamic Parameters of Umbralisib in Treatment Naïve Patients with Chronic Lymphocytic Leukemia (CLL)

Sponsor: H. Lee Moffitt Cancer Center

IND Number: **Umbralisib**
142308

Principal Investigator: Javier Pinilla-Ibarz, MD, PhD
Department of Malignant Hematology
H. Lee Moffitt Cancer Center
12902 Magnolia Drive, Tampa, FL 33612

Statistician: Qianxing Mo, PhD

This trial is supported by TG Therapeutics, Inc. (Tracking Number: TGR-NTG-006)

TABLE OF CONTENTS

STUDY SYNOPSIS

Protocol no.	MCC 19585
Study Title	A Phase 2 Study to Assess the Efficacy, Safety, Pharmacokinetic and Pharmacodynamic Parameters of Umbralisib in Treatment Naïve Patients with Chronic Lymphocytic Leukemia (CLL)
Sponsor	H. Lee Moffitt Cancer Center
IND #	**Umbralisib:** 142308
Principal Investigator	Javier Pinilla-Ibarz, MD, PhD Department of Malignant Hematology H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
Study Sites & Enrollment	• This study will be a single-center trial conducted at H. Lee Moffitt Cancer Center • Enrollment is expected to take approximately 18 months
Study Rationale	The purpose of this study is to evaluate the efficacy, safety, pharmacokinetic properties, and pharmacodynamic properties of umbralisib in treatment naïve chronic lymphocytic leukemia (CLL) patients. Umbralisib is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. Umbralisib has completed a Phase I dose escalation trial and has been administered safely at daily doses up through 1200 mg QD. In the Phase I study, 90 subjects with relapsed and refractory hematologic malignancies were treated with umbralisib, including 24 with CLL. The most commonly reported AEs (all grades, all causality) were diarrhea, nausea, and fatigue, the majority of which were Gr1/2. The only Gr≥3 AE in >10% of patients was neutropenia (13%). In the modified intention-to-treat population, which included subjects who received at least 800 mg per day of the original formulation or any dose of the micronized formulation and had at least one response assessment, 17 (85%) of 20 subjects with relapsed or refractory CLL achieved an objective response, with ten (50%) achieving an objective response per 2008 IWCLL criteria, seven (35%) achieving a partial response with lymphocytosis, and the remaining three (15%) achieving stable disease. Due to the differentiated safety profile, once-daily dosing and clinical activity in CLL with umbralisib, the primary aim of this study is to evaluate the overall response rate and progression-free survival of umbralisib, while better understanding the PK/PD profile of umbralisib.

Study Objectives	**PRIMARY OBJECTIVE** • To evaluate the overall response rate (CR + PR) **SECONDARY OBJECTIVES** • To determine the progression free survival of umbralisib in patients with CLL • To assess safety of umbralisib, tolerability and other efficacy outcomes • To determine the pharmacokinetics and pharmacodynamics of umbralisib **EXPLORATORY OBJECTIVES** • Alterations in T lymphocyte function • Alterations in B lymphocyte function • Alterations in global systemic cytokine patterns • Alteration in the myeloid cells, function

Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Have a diagnosis of B-cell CLL that has not been previously treated and now warrants treatment consistent with accepted iwCLL criteria (Hallek2018) for initiation of therapy. Any one of the following conditions constitute CLL that warrants treatment: a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or b) Massive (i.e., lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or c) Massive (i.e., ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) > 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/μL), or e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or f) Symptomatic or functional extranodal involvement (e.g. skin, kidney, lung, or spine), or g) Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection: i) Unintentional weight loss of ≥ 10% within the previous 6 months, or ii) Significant fatigue (≥ Grade 2), or iii) Fevers ≥100.5°F or 38.0°C for ≥ 2 weeks, or iv) Night sweats for ≥ 1 month. 2) Adequate organ system function, defined as follows: a) Absolute neutrophil count (ANC) ≥ 1,000/mm^3 platelet count ≥ 30,000/mm^3, (ANC ≥ 500/mm^3 and platelet count ≥ 20,000/mm^3 permitted if known marrow involvement). Growth factors are permitted at any time during the study, but not to meet eligibility criteria. b) Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) (unless diagnosed with Gilbert's syndrome). c) c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN if no liver involvement or ≤ 5 x the ULN if known liver involvement d) d) Calculated creatinine clearance > 30 mL/min (as calculated by the Cockcroft-Gault or MDRD formula, 24 hour urine Cr clearance also acceptable)

	3) ECOG performance status ≤ 2 4) Male or female ≥ 18 years of age 5) Ability to swallow and retain oral medication 6) Female patients who are not of child-bearing potential and female patients of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female patients of child-bearing potential and all male partners, and male patients must consent to use a medically acceptable method of contraception throughout the study period and for 30 days after the last dose of study drug. 7) Willingness and ability to comply with trial and follow-up procedures, and give written informed consent
Exclusion Criteria	Patients who meet any of the following exclusion criteria are not to be enrolled to this study: 1) Has ever received any form of treatment for CLL. 2) Corticosteroid therapy of > 10 mg daily or equivalent started less than 7 days prior to Cycle 1, Day 1 is prohibited. Prednisone ≤ 10 mg daily or equivalent is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted. 3) Prior treatment with umbralisib. 4) Prior treatment with autologous hematologic stem cell transplant or allogeneic hematologic stem cell transplant. 5) Evidence of chronic active Hepatitis B (HBV, not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), active cytomegalovirus (CMV), or known history of HIV. If HBc antibody is positive, the subject must be evaluated for the presence of HBV DNA by PCR. If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. See Appendix C. If the subject is CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. Subjects with positive HBc antibody and negative HBV DNA by PCR are eligible. Subjects with positive HCV antibody and negative HCV RNA by PCR are eligible. Subjects who are CMV IgM positive but who are CMV DNA negative by PCR are eligible. Antiviral prophylaxis should be considered per institutional protocol. 6) Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation / Hodgkin Lymphoma). 7) Evidence of ongoing systemic bacterial, fungal, or viral infection, except localized fungal infection of skin/nails. N O T E : Subjects may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. Use of anti-pneumocystis and antiviral prophylaxis is required. 8) Inflammatory bowel disease (such as Crohn's disease or ulcerative colitis) 9) Malabsorption syndromes 10) Irritable bowel syndrome with greater than 3 loose stools per day as a baseline. 11) Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

	a) Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV) – See Appendix B b) Myocardial infarction within 6 months of enrollment c) Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion. d) Angina not well-controlled by medication e) Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), symptomatic peripheral arterial disease, angioplasty, cardiac/vascular stenting within 6 months of enrollment. 12) Malignancy (including myelodysplastic syndromes) within 3 years of study enrollment except for basal, squamous cell carcinoma or melanoma in situ , carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer following curative treatment and with a normal PSA.. 13) Women who are pregnant or lactating. 14) Subjects requiring immediate cytoreductive therapy.
Study Design	This study is designed as a Phase 2, single-center, single-arm trial to evaluate the efficacy and safety of umbralisib, in patients with CLL. The primary objective will be measured by overall response rate (ORR). **<u>Enrollment</u>** Following Screening, qualified patients will be enrolled and receive the following: • Umbralisib 800 mg once daily within 30 minutes of a meal. During the study period, all patients will be evaluated for response by CT or MRI within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment, and at any other time point to confirm progression. Patients who fail to achieve a partial or complete response to umbralisib at the Cycle 3 assessment will discontinue study treatment. At that time, patients- will be provided appropriate options to receive established frontline therapy. Patients who demonstrate a partial or complete response will be treated until disease progression, unacceptable toxicity, or the end of the study. The primary efficacy variable will be ORR.

Statistics	The study will plan to enroll up to 40 subjects, and assuming 10% attrition, there will be approximately 35 subjects remaining for analysis. Enrollment is expected to be completed in approximately 18 months with 24 months follow- up. The ORR for the standard of care is about 60%. We expect that Umbralisib treatment could lead to 80% ORR. A Simon 2-stage minimax design that differentiates ORRs of 0.60 (null hypothesis) and 0.80 (alternative hypothesis) will be used to assess treatment efficacy, with the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) both set at 0.10. Twenty seven patients will be accrued in the first stage of the study. If 18 or fewer patients have a response, then the study will be terminated and declared negative. If 19 or more patients have a response, then an additional 8 patients will be accrued to the second stage. At the conclusion of the study, if 25 or more patients have a response out of a total of 35 patients enrolled, the regimen will be considered worthy of further investigation. Safety will be examined on an ongoing basis while the study is being conducted. Adverse events will be recorded as per CTCAE v5.0.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and Definitions of Terms	
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BM	Bone Marrow
BTK	Bruton's Tyrosine Kinase
Ca	Calcium
CBC	Complete Blood Cell Count
Cl	Clearance
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
Cmax	Maximum Concentration
CR	Complete Response
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebro-Vascular Accident
D, d	Day
DSMB	Data Safety Monitoring Board
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRG	Data Review Group
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FCR	Fludarabine, Cyclophosphamide, Rituximab
FISH	Fluorescence In-Situ Hybridization
GCP	Good Clinical Practice
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonisation
IRC	Independent Review Committee
ITT	Intent-To-Treat
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LPD	Longest Perpendicular Diameter
LTFU	Long-Term Follow Up
MRD	Minimum Residual Disease

Abbreviations and Definitions of Terms	
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Regulatory Activities
NHL	Non-Hodgkin's Lymphoma
OS	Overall Survival
ORR	Overall Response Rate
PCR	Polymerase Chain Reaction
PE	Physical Examination
PFS	Progression-Free Survival
PD	Pharmacodynamic or Progressive Disease
PK	Pharmacokinetic
PPD	Perpendicular Diameters
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SOC	System Organ Class
SPD	Sum of the Products
SUV	Standardized Uptake Value
t1/2	Half-Life of Elimination
TTR	Time to Response
ULN	Upper Limit of Normal
V	Visit
Vd	Volume of Distribution
WHO	World Health Organization

1. INTRODUCTION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

In the US, an estimated 14,620 new cases of Chronic Lymphocytic Leukemia (CLL) will be reported in 2015 with deaths totaling 4,650 due to the disease according to American Cancer Society estimates (American Cancer Society, 2015). CLL affects mainly older adults, accounts for one third of all diagnosed cases of leukemia, and is characterized by the accumulation of clonal mature B lymphocytes in the blood, bone marrow, and secondary lymphoid tissues (Lin K, 2002). CLL is a heterogeneous disease, with several higher risk cytogenetic abnormalities which are generally more difficult to treat, including 17p deletion, P53 gene mutation, and 11q deletion (Hallek M, 2008) (Lin K, 2002). Patients with 17p deletion show higher resistance to conventional chemotherapies as well as shorter duration of survival than non 17p deletion patients. Patients with 11q deletion have been associated with marked lymphadenopathy (Hallek M, 2008). Patients with P53 gene mutations are associated with an adverse clinical outcome (Lin 2002).

1.2 UMBRALISIB

Umbralisib is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K.[3]
Umbralisib also targets casein kinase-1 epsilon (CK-1Ɛ) a protein which may inhibit regulatory T- cell function.

1.1.1NOVEL MECHANISM OF ACTION

A study was done to compare the effects of umbralisib, duvelisib, and idelalisib on T cells in a CLL mouse model and analyze immune-mediated adverse events following oral administration

(Maharaj et al, ASH 2017). Peripheral Treg count was negatively correlated with incidence of toxicity in mice treated with PI3K inhibitors. Umbralisib showed decreased anti-Treg effects in a dose-dependent manner compared to other PI3K inhibitors in CLL T cells. Furthermore, umbralisib was shown to uniquely inhibit CK1e in euTCL1 T cells dose-dependently. In this way, CK1e inhibition by umbralisib may offer an explanation for less anti-Treg effects. The goal of this phase 2 study is to further analyze the relationship between PI3K delta inhibition and T cell subsets.

1.2.2 CLINICAL DEVELOPMENT OF UMBRALISIB

1.2.2.1 SINGLE-AGENT IN PATIENTS WITH RELAPSED OR REFRACTORY HEMATOLOGIC MALIGNANCIES

Umbralisib was evaluated in a single-agent Phase I dose-escalation study (Study TGR-1202-101; NCT01767766) in subjects with relapsed and refractory hematologic malignancies (Burris et al, Lancet Oncology 2018). There were 90 subjects enrolled and eligible for safety evaluation, and 73 subjects evaluable for efficacy in the modified intention to treat population. The median age was 64 years (range 51-72), 63% male, median number of prior therapies was 3, and 49% of subjects were refractory to their most recent prior therapy. Histological diagnoses included; CLL (n=24), FL (n=22), DLBCL (n=16), HL (n=11), MCL (n=6), MZL (n=5), WM (n=2), HCL and TCL (n=1 each). The
majority of subjects (58%) had received 3 or more prior therapies.

Patients were enrolled in a 3+3 dose-escalation design starting at 50 mg QD with subsequent cohorts evaluating doses as high as 1800 mg QD. In an effort to further improve the oral bioavailability of umbralisib, the particle size of the drug product was reduced through a micronization process, resulting in greater absorption when tested in a bioequivalence crossover study in healthy subjects (see Section 1.3.2.2 Healthy Subject Pharmacokinetic Studies below). This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1800 mg QD. The maximum tolerated dose (MTD) was 1200 mg QD of the micronized formulation, with 800 mg of this formulation selected as the recommended phase 2 dose based on changes in tumor burden correlated with dose-proportional plasma exposure. Intra-subject dose escalation rules allowed subjects enrolled into the study in early cohorts to increase their dose of umbralisib as subsequent higher cohorts cleared safety evaluation. The most common treatment-emergent adverse events irrespective of causality were diarrhea (in 39 [43%] of 90 subjects), nausea (38 [42%]), and fatigue (28 [31%]). The most common grade 3 or 4 adverse events were neutropenia
(in 12 [13%] subjects), anemia (eight [9%]) and thrombocytopenia (six [7%]). Serious adverse events considered at least possibly related to umbralisib occurred in seven subjects: pneumonia in three (3%) subjects, lung infection in one (1%), febrile neutropenia in one (1%), and colitis in two (2%), one of whom also had febrile neutropenia. Both cases of colitis occurred above the recommended phase 2 dose. No time-related trends in toxicity were noted. See the umbralisib investigator's brochure for a complete overview of the umbralisib side effect profile.

Dosing of umbralisib initially occurred in the fasting state, but was transitioned mid-study to fed state dosing, with subjects instructed to take umbralisib with food. All dosing of umbralisib is now conducted using the micronized formulation and in the fed state.

Among 73 subjects in the modified intention-to-treat population, which included subjects who received at least 800 mg per day of the original formulation or any dose of the micronized formulation and had at least one response assessment, 53 (73%) had reductions in disease burden, including 33 (45%) subjects with reductions of 50% or more, of which three (4%) were a complete response and 30 (41%) were a partial response. In subjects with relapsed or refractory CLL, 17 (85%) of 20 achieved an objective response, with ten (50%) achieving an objective response per 2008 IWCLL criteria, seven (35%) achieving a partial response with lymphocytosis, and the remaining three (15%) achieving stable disease. Of eight assessable subjects with CLL who had high-risk cytogenetic features, six (75%) had a response, of whom two (25%) had a partial response with lymphocytosis, and the remainder had stable disease. In subjects with follicular lymphoma, nine (53%) of 17 subjects achieved an objective response, including two (12%) who achieved a complete response; the remainder had a partial response. In subjects with diffuse large B-cell lymphoma, four (31%) of 13 achieved an objective response and two (15%) further subjects achieved stable disease. Responses for the other subject subgroups were Hodgkin lymphoma: one complete response, four stable disease, four progressive disease; marginal zone lymphoma: one partial response, four stable disease; Waldenström's macroglobulinemia: two stable disease; and mantle cell lymphoma: one partial response, four stable disease, and one progressive disease. In a post-hoc exploratory analysis, tumor reductions in most subjects with indolent lymphoma and CLL treated with umbralisib tended to improve over time. The mean duration of response was 13.4 months (95% CI 7.7–19.1) in 16 subjects in the CLL cohort, 6.4 months (4.5–17.3) in four subjects in the DLBCL cohort, and 9.3 months (3.6–15.1) in nine subjects in the follicular lymphoma cohort. In a post-hoc exploratory analysis of progression-free survival, median progression-free survival was 24.0 months (95% CI 7.4 months–not reached) in 20 subjects with CLL, and 16 months (9.2 months–not reached) in 24 subjects with indolent non-Hodgkin lymphoma (follicular lymphoma, Waldenström's macroglobulinemia, and marginal zone lymphoma). Overall, umbralisib was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts. Umbralisib monotherapy is being studied in a registration directed trial in various NHL subtypes (Study UTX-TGR-205 [UNITY-NHL]; NCT02793583). The combination of ublituximab and umbralisib is also being studied in Study UTX-TGR-205 [UNITY-NHL]; NCT02793583) and in another registration directed trial in CLL (Study UTX-TGR-304 [UNITY-CLL]; NCT02612311). See the latest Investigator's Brochure for updated information regarding the clinical development of umbralisib.

1.3 RATIONALE FOR THE PHASE 2 TRIAL

Previously, umbralisib has been demonstrated to be safe and efficacious in the treatment of CLL as part of a broad Phase 1 study enrolling a variety of hematologic malignancies (Burris et al, Lancet Oncology 2018). While clinically active, the mechanism of action for umbralisib and the mechanism underlying its unique safety profile remain unclear. Previous studies in mice demonstrated inhibition of pAKT suggesting activity through inhibition of the PI3K pathway, however recently the CK1e targeting properties of umbralisib which may have a T-cell supportive role have also been described in pre-clinical models. The goal of this study is to further describe the safety and efficacy profile, while characterizing the pharmacodynamic properties of umbralisib in relation with pharmacokinetics.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

PRIMARY OBJECTIVE

- To evaluate the overall response rate (CR + PR)

SECONDARY OBJECTIVES

- To determine the progression free survival of umbralisib in patients with CLL
- To assess safety of umbralisib, tolerability and other efficacy outcomes
- To determine the pharmacokinetics and pharmacodynamics of umbralisib

EXPLORATORY OBJECTIVES

- Alterations in T lymphocyte function, including changes in:
    a. TH1:TH2 polarization, and Treg:TH17 distributions
    b. Markers of T cell exhaustion and/or inhibition
    c. Alterations in distribution of naïve vs. memory
    d. Cellular activation and cell-mediated cytotoxic capacity
- Alterations in B lymphocyte function, including changes in:

a. Change in the B cell receptor repertoire, perhaps clonal evolution

b. Quantitative serum immunoglobulin levels and subtyping

c. Fc-receptor (FcR) expression patterns

- Alterations in global systemic cytokine patterns: Includes IFN-γ, TNF-α, IL-2, IL-4, IL-10, IL-6, IL-17A, allowing discrimination between TH1, TH2, TH17 and Treg profiles
- Alteration in the Myeloid cells, function, including changes in:

  -Antigen presentation capacity (Functional assay)

  -Alterations in the distribution of M1 vs M2 & N1 vs N2

- Pharmacodynamics analysis, including pAKT changes in:

  -T cell compartment

  -B cell compartment

Samples (blood, bone marrow, etc.) may not be taken from subjects and stored for future research that is not defined within this protocol without a contractual agreement between the institution and TG Therapeutics, Inc. to govern the ensuing research prior to its conduct.

1.3 EFFICACY ENDPOINTS

Overall response rate (ORR)
ORR is defined as sum of CR and PR rates.

Progression-free survival (PFS)
PFS is defined as the interval from registration to the earlier of the first documentation of definitive disease progression or death from any cause.

Definitive disease progression based on standard criteria (Hallek et al. 2018) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis.

Complete Response (CR) Rate
CR rate is defined as the proportion of patients who achieve a CR.

Minimal Residual Disease (MRD) Negativity Rate
MRD negativity rate is defined as the proportion of patients who are MRD negative.

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

3. ELIGIBILITY CRITERIA

Patients must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for participation in this study.

3.1 INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Have a diagnosis of B-cell CLL that has not been previously treated and now warrants treatment consistent with accepted iwCLL criteria (Hallek 2018) for initiation of therapy. Any one of the following conditions constitute CLL that warrants treatment:
   a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or
   b) Massive (i.e., lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or
   c) Massive (i.e., ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or
   d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) >50% over a 2-month period or lymphocyte doubling time of <6 months (as long as initial ALC was ≥30,000/μL), or
   e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or
   f) Symptomatic or functional extranodal involvement (e.g. skin, kidney, lung, or spine), or
   g) Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
      i) Unintentional weight loss of ≥10% within the previous 6 months, or
      ii) Significant fatigue (≥ Grade 2), or
      iii) Fevers >100.5°F or 38.0°C for ≥2 weeks, or
      iv) Night sweats for >1 month.
2) Adequate organ system function, defined as follows:
   a) Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3 platelet count $\geq$ 30,000/mm^3, (ANC ≥ 500/mm^3 and platelet count ≥ 20,000/mm^3 permitted if known marrow involvement). Growth factors are permitted at any time during the study, but not to meet eligibility criteria.
   b) Total bilirubin ≤1.5 times the upper limit of normal (ULN) (unless diagnosed with Gilbert's syndrome).
   c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement
   d) Calculated creatinine clearance >30 mL/min (as calculated by the Cockcroft-Gault or MDRD formula, 24 hour urine Cr clearance also acceptable)
3) ECOG performance status ≤ 2
4) Male or female ≥ 18 years of age
5) Ability to swallow and retain oral medication
6) Female patients who are not of child-bearing potential and female patients of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female patients of child-bearing potential and all male partners, and male patients must consent to use a medically acceptable method of contraception

throughout the study period and for 30 days after the last dose of study drug.

7) Willingness and ability to comply with trial and follow-up procedures, and give written informed consent

3.2 EXCLUSION CRITERIA

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

1) Has ever received any form of treatment for CLL.
2) Corticosteroid therapy of prednisone > 10 mg or equivalent started at least 7 days prior to Cycle 1, Day 1 is prohibited. Prednisone ≤ 10 mg daily or equivalent is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted.
3) Prior treatment with umbralisib.
4) Prior treatment with autologous hematologic stem cell transplant or prior Allogeneic hematologic stem cell transplant is excluded.
5) Evidence of chronic active Hepatitis B (HBV, not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), active cytomegalovirus (CMV), or known history of HIV. If HBc antibody is positive the subject must be evaluated for the presence of HBV DNA by PCR. If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. See Appendix C. If the subject is CMV IgG or CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. Subjects with positive HBc antibody and negative HBV DNA by PCR are eligible. Subjects with positive HCV antibody and negative HCV RNA by PCR are eligible. Subjects who are CMV IgG or CMV IgM positive but who are CMV DNA negative by PCR are eligible. Antiviral prophylaxis should be considered per institutional protocol.
6) Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation / Hodgkin Lymphoma).
7) Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infection of skin/nails. NOTE: Subjects may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. Use of anti-pneumocystis and antiviral prophylaxis is required.
8) Inflammatory bowel disease (such as Crohn's disease or ulcerative colitis)
9) Malabsorption syndromes
10) Irritable bowel syndrome with greater than 3 loose stools per day as a baseline.
11) Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    a) Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV) – See Appendix B
    b) Myocardial infarction within 6 months of enrollment
    c) Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.
    d) Angina not well-controlled by medication
    e) Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), symptomatic peripheral arterial disease, angioplasty, cardiac/vascular stenting within 6 months of enrollment.
12) Malignancy, including myelodysplastic syndromes, within 3 years of study enrollment

except for basal, squamous cell carcinoma or melanoma in situ, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer following curative treatment and with a normalPSA level

.

13) Women who are pregnant or lactating.

14) Subjects requiring immediate cytoreductive therapy.

4. STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This study is designed as a Phase 2, single-center, single-arm trial to evaluate the ORR and PFS of umbralisib in treatment naïve CLL patients requiring therapy. Daily doses of oral umbralisib will be administered in the absence of disease progression, unacceptable toxicity, or withdrawal from treatment. Treatment cycles are 4 weeks, with the efficacy evaluations within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment, and at any other time point to confirm progression. Patients who fail to achieve a partial or complete response to umbralisib at the Cycle 3 assessment will discontinue study treatment. At that time, patients- will be provided appropriate options to receive established frontline therapy. Patients who demonstrate a partial or complete response will be treated until disease progression, unacceptable toxicity, or the end of the study. Enrollment will be up to 35 patients.

4.2 REGISTRATION/ENROLLMENT

Following Screening, qualified patients will receive the following:

- Umbralisib 800 mg once daily

During the study period, all patients will be evaluated for response by CT or MRI within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment, and at any other time point to confirm progression. Patients who fail to achieve a partial or complete response to umbralisib at the Cycle 3 assessment will discontinue study treatment. At that time, patients- will be provided appropriate options to receive established frontline therapy. Patients who demonstrate a partial or complete response will be treated until disease progression, unacceptable toxicity, or the end of the study.

4.3 STUDY SITES

This is a single-center study. Enrollment is expected to be completed in approximately 18 months.

4.4 DISCONTINUATION FROM STUDY TREATMENT

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Failure to achieve a partial or complete response to umbralisib at the Cycle 3 assessment
- Intolerable toxicity related to study drug
- Patient requests to withdraw consent or discontinue treatment
- Pregnancy
- Inability of the patient to comply with study requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Non-compliance/lost to follow-up
- Investigator discretion
- Discontinuation of the study

Patients who discontinue from study treatment prior to Cycle 12 (for reasons other than progressive disease) should continue to be followed for progression approximately every 3 months up until the time Cycle 12 would have occurred, then approximately every 6 months.

Patients who discontinue from study treatment after Cycle 12 for reasons other than disease progression should be followed for progression approximately every 6 months.

After withdrawal from protocol treatment, patients should be followed for AEs for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case the investigators must record his or her reasoning for this decision in the patient's medical records.

All patients who have CTCAE Grade 3 or 4 laboratory abnormalities at the time of withdrawal should be followed until the laboratory values have returned to Grade 1 or 2, unless in the opinion of the investigator, it is not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patient's medical records.

All patients that begin therapy outside of the scope of this protocol within 30 days of discontinuing umbralisib do not need to be followed for AEs, unless umbralisib is determined to be the direct cause of the AE in the opinion of the treating investigator. After 30 days from discontinuation of umbralisib, these AEs no longer need to be followed.

5. STUDY ASSESSMENTS AND TREATMENT SCHEDULE

The table below lists all required assessments that should be performed at each study visit.

STUDY ASSESSMENTS AND TREATMENT SCHEDULE

All cycles are 28 day cycles	Screening	Cycle 1[1]				Cycles 2 - 6[2]	> Cycle 6[3]	End of Treatment	F/U	End of Study
	D-28 to D0	D1	D2	D8	D15	D1	Every 3 cycles			
Medical History	X									
ECOG Performance Status	X	X								
Physical Examination/Vitals	X	X		X	X	X	X	X	X	X
EKG (QTcF)	X									
Serology HCV, HBV, CMV	X[4]									

CMV surveillance[4]						X[4]	X[4]	X[4]		
Hematology	X	X		X	X	X	X	X	X	X
Chemistry	X	X		X	X	X	X	X	X	X
PT/INR, PTT	X									
β_2-Microglobulin	X									
CT Imaging (neck, chest, abdomen, pelvis)	X[5]	Within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment, and at any other time point to confirm progression								
Response assessment[5]						X[5]	X[5]	X[5]	X[5]	X[5]
Serum Pregnancy Test	X[6]									
FISH + IgHV	X									
Correlative Labs (PBMC)[7]		X				X[8]	C7 only X[8]	Disease progression		
PKs[8]		X	X			X				
Bone Marrow aspirate for correlative studies [9]	X						X[12]			
PDs[8]		X				X				
Umbralisib 800 mg		Daily Days 1 – 28								
Bone Marrow Biopsy[9,10]	X						X			
AE Assessment		X		X	X	X	X	X		

[1] Visit days and all related assessments and testing have +/- 1 day window in Cycle 1.

[2] Unless otherwise noted (i.e. CT scans), visit days and all related assessments and testing have +/- 3 day window in Cycles 2 - 6.

[3] Unless otherwise noted (i.e. CT scans), visit days and all related assessments and testing have +/- 7 day window for Cycles > 6.

[4] Serum virology to include HBsAg, HBc antibody, HCV antibody, CMV IgG and CMV IgM. If HBc antibody is positive, the subject must be evaluated for the presence of HBV DNA by PCR - See Appendix C. If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. If the subject is CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. CMV surveillance by PCR every 3 cycles while receiving study treatment. In addition, a final CMV test by PCR should be done upon treatment discontinuation.

.

[5] Baseline CT scan within 30 days prior to Cycle 1, Day 1; then within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment. Additional scans may be requested at the discretion of the investigator at any other time point to confirm progression (all scans +/-14 days). CT imaging should be performed at EOT visit if it hasn't been completed within past 30 days.

[6] Serum pregnancy test within 3 days prior to starting treatment on Cycle 1, Day 1 for women of childbearing potential.

[7] Peripheral Blood Mononuclear Cells (PBMC) – Peripheral blood sample to be obtained pre-dose on C1D1, C2D1, C4D1, C7D1, C13D1 and at the time of disease progression, which may occur at any time point including at the End of Treatment visit or the End of Study visit..

[8] PK samples (plasma) will be collected according to the schedule in Section 5.1.2. Additional PK samples may be collected outside of this schedule upon the occurrence of toxicity in order to correlate to plasma concentrations. PD samples (fresh peripheral blood) will be collected according to the schedule in Section 5.1.2. PBMCs will be isolated by Ficol centrifugation and B and T cell will be analyzed (post ex vivo stimulation) for phosphorylation of AKT.

[9] An aspirate sample of 8-10 ml will be obtained at the time of each bone marrow biopsy- screening and the end of C12- for correlative studies.

[10] Bone Marrow aspirate/biopsy performed at baseline and within 14 days following the last dose of Cycle 12 study drug.. (Research lab Cycle 13

5.1.1 LABORATORY ASSESSMENTS

Laboratory assessments will be collected as specified in the study assessments and treatment schema

5.1.1 LOCAL LABORATORY ASSESSMENTS

1. Hematologic profile and serum chemistry to include through Cycle 6:

Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	Absolute lymphocyte count

Erythrocyte count	Monocytes	Leukocyte count
Basophils	Eosinophils	Absolute neutrophil count
Serum Chemistry		
Albumin	Creatinine	SGOT [AST]
Alkaline phosphatase	Glucose	SGPT [ALT]
Bicarbonate (total CO_2)	LDH	Sodium
BUN	Magnesium	Total bilirubin
Calcium	Phosphorus	Total protein
Chloride	Potassium	Uric acid

Hematologic and Serum Chemistry windows as follows:

- Cycle 1: -1 day window
- Cycles 2 – 6: +/- 3 day window

2. After Cycle 6, required labs will include a standard CBC/differential and chemistry as below:

Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	Absolute lymphocyte count
Erythrocyte count	Monocytes	Leukocyte count
Basophils	Eosinophils	Absolute neutrophil count
Serum Chemistry		
Albumin	Creatinine	SGOT [AST]
Alkaline phosphatase	Glucose	SGPT [ALT]
Bicarbonate (total CO_2)	LDH	Total protein
BUN	Sodium	
Calcium	Total bilirubin	
Chloride	Potassium	

- Cycle 6: +/- 7 day window

3. Serum β-HCG test during screening for women of childbearing potential as outlined in Section 5, STUDY ASSESSMENTS AND TREATMENT SCHEDULE.

4. Serum Virology to include HBsAg, HBc antibody, HCV antibody, and CMV IgG and CMV IgM. If HBc antibody is positive, the subject must be evaluated for the presence of HBV DNA by

[13] Patients who discontinue study drug should have a follow up visit or telephone call to assess for AEs. This should be done 30 days (+/- 7 days) after the last dose of study drug. In addition, SAEs will be reported for 30 days after the last dose of study drug. (see section 10.4.3)

PCR. If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. See Appendix C. If the subject is CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. CMV surveillance by PCR every 3 cycles while receiving study treatment. In addition, a final CMV test by PCR should be done upon treatment discontinuation. See Section 5.

5. Baseline bone marrow aspirate/biopsy within 30 days prior to Cycle 1, Day 1, then follow Section 5 table, footnotes 11 and 12.

6. β_2-microglobulin at screening only.

7.Coagulation lab tests to include PT/INR and PTT.

8. Fluorescence in situ hybridization (FISH) of peripheral blood for 13q deletion, 11q deletion, 17p deletion, trisomy 12, t(11:14).

9. DNA sequencing for IgHV mutation status.

5.1.2 CENTRAL LABORATORY ASSESSMENTS

The PK parameters (including $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, λ_z, and $t_{½}$) of umbralisib will be assessed by analysis of umbralisib plasma concentrations.

PK blood (plasma) samples will be taken at the following timepoints.

TABLE 1 PHARMACOKINETIC COLLECTION TIMES

Visit	Scheduled time point
Cycle 1, Day 1	Pre-dose
	0.5 hour post dose (± 5 minutes)
	1 hour post dose (± 10 minutes)
	2 hours post dose (± 10 minutes)
	4 hours post dose (± 30 minutes)
	6 hours post dose (± 30 minutes)
Cycle 1, Day 2	Pre-dose, 24 hours post Day 1 dose (± 2 hours)
Cycle 2, Day 1	Pre-dose
	2 hours post dose (± 10 minutes)
	4 hours post dose (± 30 minutes)
Cycle 3, Day 1	Pre-dose
Cycle 4, Day 1	Pre-dose
Cycle 5, Day 1	Pre-dose
Cycle 6, Day 1	Pre-dose

5.1.3 PHARMACODYNAMICS

The analyses for pharmacodynamic biomarkers are exploratory and will not be used to guide treatment decisions.

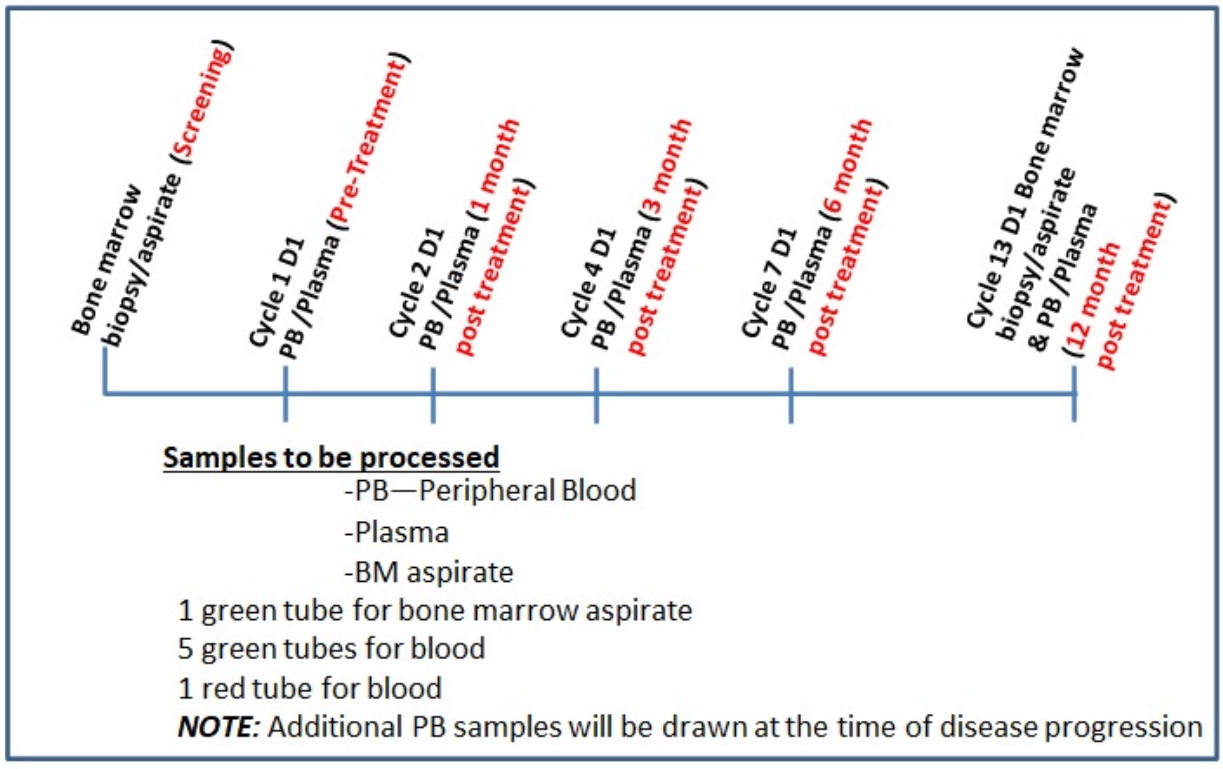
PHARMACODYNAMIC COLLECTION TIMES

Visit	Scheduled time point (hours)
Cycle 1, Day 1	Pre-dose
	2 Hours Post-dose
	4 Hours Post-dose
	6 Hours Post-dose
Cycle 2, Day 1	Pre-dose
	2 Hours Post-dose
	4 Hours Post-dose
Cycle 3, Day 1	Pre-dose
Cycle 4, Day 1	Pre-dose
Cycle 5, Day 1	Pre-dose
Cycle 6, Day 1	Pre-dose

5.1.4 CORRELATIVE STUDIES (EXPLORATORY OBJECTIVE)

Biological samples (Peripheral blood) will be collected at up to 6 time-points outlined in Section 5, STUDY ASSESSMENTS AND TREATMENT SCHEDULE. Each red top tube will be 10 ml of peripheral blood. Each green top tube will be 10 ml of peripheral blood. Bone Marrow aspirate will be collected at baseline and the end of Cycle 12. Each aspirate sample will be 8-10 ml of aspirate. As the correlative experiments are not the primary focus of the study and are more exploratory in nature, no sample size / power calculations were completed. Summary statistics will be used to summarize the quantitative measures (e.g., cytokine levels, expression levels) for the patients at the specified time-points with two-sample t-test use to determine if quantitative measurements differ between patients that respond and patients that do not respond at each time point. When assessing changes in quantitative measurements between time-points (e.g., pre and post treatment measurements) paired t-tests will be used. Longitudinal analysis with linear mixed models will also be used to look for statistical differences between the responders and non-responders using quantitative measurements at all time-points. Correlation between quantitative measurements will be assessed with Spearman correlation.

If correlative lab samples are drawn at a required time point and treatment is delayed, the sample may be retained. When the subject re-starts the cycle, the sample will be re-collected for continuity with other subject samples. The research lab will be notified of the event if the treatment is delayed.



Immune-Profiling Studies

1. T cell function will be assessed for changes in multiple characteristics including memory formation, TH-polarity, markers of exhaustion, and activation via flow cytometric analysis. Naïve and memory sub-populations will be defined according to expression of CD45RA, CD62L, CCR5 and CCR7. TH-polarization, including TH1, TH2, TH17 and Treg subsets, will be determined by intracellular cytokine and FoxP3 profiles. Changes in T cell exhaustion phenotype will be tracked in terms of surface expression of several well-defined markers, including CD160, CD200R, CD244, CD272, CD274, CD279, as well as the intracellular markers Lag3 and Tim3. Alterations in cellular activation will be measured in terms of phosphorylation of critical T cell signaling pathways, STAT 1, 3 and 5, as well as by surface expression of CD107a, correlating to secretory/cytotoxic activity.

2. Global Immune function will be assessed. A) Patient peripheral blood will be assessed by multi parameter flow analysis for myeloid cells—specifically myeloid derived suppressor cells MDSCs both PMN-MDSCs and M-MDSCs using the following markers: CD3, CD14, CD19, CD56 HLA-DR, CD33, CD15, CD66b, and CD11b. B) Patient sera will be evaluated by flow cytometric means using cytokine bead arrays to measure serum cytokine levels quantitatively. The cytokine panel

   will include IFN-γ, TNF-α, IL-2, IL-4, IL-10, IL-6, IL-17A, allowing discrimination between TH1, TH2, and TH17 profiles.

3. Peripheral blood to collect DNA and RNA will be processed for future assessments.

4. Pharmacodynamics analysis of pAKT expression (Phos-Flow) for collected samples over time point of continued study.

5 6 TREATMENT PLAN

6.1 TREATMENT SUMMARY

Treatment will be administered on an outpatient basis in 4-week (28 day) cycles.

Umbralisib

6.1.1 - 800 mg umbralisib once daily within 30 minutes of a meal until removal from study

6.12- Patient diary will be utilized

6.2AGENT ADMINISTRATION

Umbralisib will be self-administered orally, all on an outpatient basis.

6.2.1 GUIDELINES FOR ADMINISTRATION OF UMBRALISIB

- *Method of Administration:* Umbralisib will be administered orally once daily within

30 minutes of a meal.

- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Anti-microbial prophylaxis:* Patients are required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy prior to Cycle 1, Day 1.
    - *Anti-viral Prophylaxis*: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent.
    - *PCP Prophylaxis:* Final choice of PCP prophyalxis is per investigator discretion.

    Final choice of PCP and anti-viral prophylaxis therapy is per investigator discretion. If PCP or anti-viral therapy is not tolerated, alternate to a different PCP or anti-viral therapy, reduce the dose or modify the schedule for the prophylactic agent, or discontinue prophylaxis at investigator discretion.
- *Pre-medications:* None

Umbralisib will be stored in the Moffitt Investigational Pharmacy Department. It will be dispensed at the site by the clinical research staff under the direction of the PI or by a pharmacist at the site. Patients must be provided drug in its original container. Patients should be instructed to return all empty and partially filled bottles including any unused tablets when they return the site. Any unused study drug will be destroyed on site per Investigational Pharmacy standard procedures. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle and as needed. Missed doses will be documented in the patients' medical record.

Umbralisib will be self-administered (by the patient). Tablets should be taken at approximately the same time each day with food (within 30 minutes of a meal). Patients should be instructed to swallow the tablets whole and should not chew or crush them.

If a dose of umbralisib is missed, it should be taken as soon as possible on the same day. If it is missed for greater than 12 hours, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

6.2.1.1 DISPENSING OF UMBRALISIB

Before dispensing, the site pharmacist or his/her representative must check that the umbralisib is in accordance with the product specifications and the validity is within the re-test date.

The exact dose and the date of administration of umbralisib must be recorded within the patient's medical records. Any error in drug administration should be recorded (e.g., missed dose).

The Investigational Pharmacist or his/her representative should complete the accountability record with information concerning the dispensation of umbralisib.

If a subject requires a dose reduction, the site pharmacist will dispense only the number of bottles of study drug required for the subject to have an adequate supply until the next dispensing visit.

6.2.2 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that patient has:

- No intolerable toxicities related to study drug.
    - Treatment may be delayed to recover from toxicity for a maximum of eight weeks. Treatment delays of greater than 8 weeks may be allowed after discussion with the Principal Investigator.
- No clinical or radiographic evidence of disease progression.
- Not withdrawn from the study for other reasons.

6.3 DOSING DELAYS AND MODIFICATIONS

Patients should be assessed clinically for toxicity at each visit using the NCI CTCAE v5.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) grading scale. Dose delay and/or modification guidance is for adverse events considered at least possibly related to the study drug. If cytopenias are deemed related to the underlying disease rather than study drug, dose modifications are not required, or are per investigator discretion.

Umbralisib should be discontinued if treatment is delayed for greater than 8 weeks due to toxicity unless the Principal Investigator approves restarting treatment. If the subject discontinues treatment but has not progressed, the subject should be followed for progression. If a patient withdraws consent or has documented progression, an end of study visit should be completed.

6.3.1 DOSE DELAY/MODIFICATIONS: UMBRALISIB

TABLE 2: UMBRALISIB DOSE DELAY AND/OR MODIFICATIONS GUIDANCE

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 2 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 3 neutropenia	Maintain current dose, consider supportive care. If neutropenia recurs or persists at Grade 3 for more than 14 days , stop umbralisib until grade ≤ grade 2 and resume at next lower dose level.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay umbralisib until Grade ≤ 3 and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider supportive care. If delay is >8 weeks, permanently discontinue umbralisib. If recurrence after rechallenge, resume at next lower dose level.
Thrombocytopenia	
Grade ≤ 3 thrombocytopenia	Maintain current dose level and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay umbralisib until Grade ≤ 3; thereafter, resume at full dose. Consider supportive care intervention as warranted. If recurrence after rechallenge, resume at next lower dose level. If delay is > 8 weeks, permanently discontinue umbralisib.
Pulmonary & Related Infections*	

Grade 1 & 2	Stop all therapy and hold until complete resolution. Restart umbralisib at one lower dose level. If recurrence after rechallenge, discontinue all treatment therapy. If delay is > 8 weeks, permanently discontinue umbralisib.
Grade ≥ 3	Discontinue all therapy
*** For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at investigator's discretion. While pneumonitis has been minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-herpetic viral prophylaxis is required prior to starting umbralisib.**	
Diarrhea and/or Colitis	
Diarrhea Grade ≤ 2	Maintain current dose level if tolerable or hold and then resume at current dose level once has resolved. **NOTE**: If persistent Grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ Grade 1. If recurrence after rechallenge, resume at next lower dose level. If delay is > 8 weeks, permanently discontinue umbralisib.
Diarrhea Grade ≥ 3	Withhold umbralisib until Grade ≤ 2. If recurrence after rechallenge, resume at next lower dose level. If delay is > 8 weeks, permanently discontinue umbralisib.
Colitis (all Grades)	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level If delay is > 8 weeks, permanently discontinue umbralisib.
Liver Toxicity (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Grade 1	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Monitor labs every 1-2 weeks.
Grade 2	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Begin supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent per investigator discretion) **. Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off. If liver toxicity recurs to Grade 2: o Re-initiate steroids. o Monitor labs at least weekly until Grade 1. o Consider delaying umbralisib. o Once resolved to Grade ≤1 o If umbralisib was delayed, restart umbralisib at current dose. o Taper prednisone by 10 mg per week until off. If umbralisib is delayed for > 8 weeks, permanently discontinue umbralisib.

Grade ≥ 3	Delay umbralisib. Assess concomitant medications and risk factors*. Begin/continue supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent per investigator discretion) **. Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1: ○ Restart umbralisib at one lower dose level. ○ Taper prednisone by 10 mg per week until off. If umbralisib is delayed for > 8 weeks, permanently discontinue umbralisib
* Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc. **Supportive Care – Aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc. Important: Before initiating steroids, check for viral hepatitis or CMV infection.	
All Other Non-Hematological Adverse Events	
Grade ≤ 2	Maintain current dose level
Grade ≥ 3	Withhold umbralisib until Grade ≤ 2. If recurrence after rechallenge, resume at the next lower dose level. If delay is > 8 weeks, permanently discontinue umbralisib.

TABLE 3: STUDY DRUG DOSE LEVELS

Study Drug	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Umbralisib	800 mg	600 mg	400 mg

A maximum of two dose level reductions are allowed for umbralisib. If a patient requires a dose reduction of umbralisib due to study drug related toxicity, the dose may not be re-escalated. If further evaluation of the toxicity reveals the event was not related to umbralisib, this should be recorded in the medical record and dose re-escalation to the next higher dose level may be considered at the discretion of the investigator.

6.4 ORDERING UMBRALISIB

Umbralisib is available from TG Therapeutics. Please allow 5 to 7 business days between drug ordering and drug arrival. Please direct drug orders to ISTdrugorder@tgtxinc.com. The email should include the following:

- Requested quantity of TG Therapeutics study drug(s)
- Principal Investigator name
- Study title
- Investigational drug pharmacy shipping address

Upon receipt of treatment supplies, the Pharmacist or the appropriate person of the site should update the accountability forms for umbralisib. If any abnormality on the supplied bottles (umbralisib) is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact TG Therapeutics.

6.5 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment should continue through Cycle 1 and beyond unless one of the following criteria applies:

- Disease progression or inter-current illness that prevents further treatment.
- Patient decides to withdraw from the study, or changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Study drug will be made available to responding patients until disease progression. If umbralisib becomes commercially available during the active period on study, an attempt will be made to obtain this agent through commercial insurance. If study drug continues past cycle 12, any laboratory or other testing procedures will be ordered at physician discretion and not considered a study procedure. Adverse events will be collected during this time, per guidance in Section 10.4.3.

During the study period, all patients will be evaluated for response by CT or MRI within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment, and at any other time point to confirm progression. Patients who fail to achieve a partial or complete response to umbralisib at the Cycle 3 assessment will discontinue study treatment. At that time, patients- will be provided appropriate options to receive established frontline therapy. Patients who demonstrate a partial or complete response will be treated until disease progression, unacceptable toxicity, or the end of the study.Patients who discontinue from study treatment and have not progressed should continue to be followed for progression, if agreeable, approximately every 3 months. If the patient discontinues after Cycle 12 for reasons other than disease progression, they should continue to be followed for progression approximately every 6 months.

6.6 STOPPING RULES

In order to allow periodic review of safety data to ensure safety and limit potential toxicity, enrollment shall be conducted in consecutive groups of 10 patients. The Principal Investigator (PI), Sub-Investigators, and the Moffitt Protocol Monitoring Committee (PMC) will be charged with reviewing safety data. Serious adverse events (SAEs) from this protocol will be reported to the IRB per their guidelines and concurrently to the PMC for review. Following the final treatment dose in Cycle 3 (Day 28 of Cycle 3) of the last patient in a group set of 10 patients, the PI and PMC will decide whether or not it is possible to proceed to enroll the next group of 10 patients. In order to ensure safety and limit toxicity for enrolled patients, dose modifications will be performed according to the schema described in Section 6.3.1. This trial will be continuously monitored by the PI and the research team as well as being reviewed for safety at the weekly Lymphoma Section Research Meeting. All serious and non-serious adverse events will be documented, managed with protocol-permitted dose reductions, followed until resolution or stabilization, and will also be reviewed by the PI, PMC and Sub-Investigators at the end of each group of 10 patients.

In the event that >20% of patients (i.e. 3 of 10 patients, 5 of 20 patients, 7 of 30 patients, etc.) discontinue therapy due to a treatment-related serious adverse event or immune mediated toxicity (e.g. transaminitis, pneumonitis, rash, or colitis), study accrual will be suspended pending further investigation, and will only be resumed at the recommendation of the PI, PMC and the Sub-Investigators.

In the event of one (1) death attributed to the study drug, study accrual will be suspended pending further investigation, and will only be resumed at the recommendation of the PI, PMC, and the Co-

Investigators. The PI, PMC, and the Sub-Investigators will have discretion to terminate the trial if an additional death occurs that can be attributed to the study drug.

7 STUDY MEDICATION OVERVIEW AND SAFETY

7.1 UMBRALISIB

Chemical Name:	Umbralisib
Other Names:	TGR-1202
Classification:	Dual inhibitor o phosphatidylinositol-3-Kinase (PI3K) Delta and Casein kinase-1 epsilon (CK-1 E)
Formulation:	See Investigator Brochure
Mode of Action:	Irreversibly inhibits activity of the Class I Delta isoform of PI3K
How Supplied:	200 mg tablets
Storage:	Store in a secured limited-access area between 20° and 25°C. Excursions permitted 15°C to 30°C.Do not freeze
Stability:	Expiration memorandums will be provided noting lot expiration dates. For questions about product expiry email productquality@tgtxinc.com
Route of Administration:	Oral
Packaging:	Umbralisib is provided in HDPE bottles each containing 30 tablets and a silica gel canister as a desiccant.
Availability:	Umbralisib is available from TG Therapeutics.

7.1.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The Investigator's Brochure (IB) is the primary source for safety information. The umbralisib IB includes a summary of adverse event data and discussion on potential risks that have been observed or may be predicted to occur with this study drug. Refer to the most recent IB, which is updated periodically, for current information on umbralisib.

7.1.1.1 VERY COMMON ≥ 10%

- **Blood and Lymphatic System Disorders:** neutropenia
- **Gastrointestinal Disorders**: Diarrhea, Nausea, vomiting

7.1.1.2 **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:** FATIGUE COMMON ≥ 2% AND < 10%

- **Blood and Lymphatic System Disorders:** anemia, thrombocytopenia, leukocytosis, lymphocytosis
- **Ear and Labyrinth Disorders:** tinnitus

- **Eye Disorder:** vision blurred
- **Gastrointestinal Disorder:** constipation, abdominal pain, abdominal distension, dyspepsia, colitis, dry mouth
- **General Disorders and Administration Site Conditions:** pyrexia, oedema peripheral
- **Infections and Infestations:** pneumonia, oral candidiasis
- **Injury Poisoning and Procedural Complication:** contusion
- **Investigations:** weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
- **Metabolism and Nutrition Disorders:** decreased appetite, dehydration, hyperglycaemia, hypokalaemia, hypophosphatemia
- **Musculoskeletal and Connective Tissue Disorder**: muscle spasms, pain in extremity
- **Nervous System Disorders**: dizziness, headache, dysgeusia, tremor

- **Nervous System Disorders: dizziness, headache,** dysgeusia, tremor
- **Psychiatric Disorders:** insomnia
- **Respiratory, Thoracic and Mediastinal Disorders:** cough
- **Skin and Subcutaneous Tissue Disorders:** rash maculo-papular, alopecia, night sweats, pruritus, rash

8 MEASUREMENT OF EFFECT

During the study period, all patients will be evaluated for response by CT or MRI within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment, and at any other time point to confirm progression. The determination of response and progression will be based on iwCLL criteria (Hallek M, 2018).

Patients who fail to achieve a partial or complete response to umbralisib at the Cycle 3 assessment will discontinue study treatment. At that time, patients- will be provided appropriate options to receive established frontline therapy. Patients who demonstrate a partial or complete response will be treated until disease progression, unacceptable toxicity, or the end of the study.
Patients with a response should 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 as per the protocol.

8.1 METHOD OF ASSESSMENT

In addition to clinical examination, radiographic evaluation will be used in all patients enrolled. All baseline assessments to characterize disease will be performed within 30 days of Cycle 1, Day 1, prior to initiation of therapy. CT scan with iodinated IV contrast is the preferred method for radiographic tumor assessment. If iodinated contrast is contraindicated, a non-contrast chest CT coupled with a gadolinium-enhanced MRI of the abdomen, pelvis and neck is an acceptable substitute. Chest x-ray, ultrasound, endoscopy, laparoscopy, PET, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (e.g.,

scan type, patient position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. However, if a patient is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless medically contraindicated.

All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification.

8.2 RESPONSE REVIEW

The review of radiographic and clinical data by the study investigators will be performed on an ongoing basis. De-identified images should be available if TG Therapeutics requests to confirm any objective response observed.

8.3 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

8.3.1 TARGET LESIONS

At baseline, up to 6 lymph nodes should be selected as target lesions (if measurable disease is present) that will be used to quantitate the status of the disease during study treatment. Ideally, the target lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as target lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

Target lesions should be measured and recorded at baseline and as per the study assessment schedule. The cross-sectional dimensions (the largest cross-sectional diameter, i.e., the LD × LPD) will be recorded (in cm) for each target lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each target lesion and the sum of the products (SPD) (in cm^2) for all target lesions will be calculated and recorded. The baseline SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a measurable nodal target lesion if it is > 1.5 cm in the longest diameter (Hallek M, 2018).

Progressive disease will be determined using the 2018 iwCLL criteria. Transient increases of lymph node size during treatment with novel inhibitors may occur (Hallek M, 2018).

8.3.2 SPLEEN AND LIVER

Both the spleen and liver will be assessed by CT/MRI scan and/or by physical examination (method of measurement should be consistent throughout study participation) at baseline and as per the study assessment schedule. The baseline and nadir values for the longest vertical dimension (LVD) of each organ will be used as reference to further characterize the objective tumor response of the measurable dimensions of the CLL during treatment. All spleen and liver

LVD measurements should be recorded in centimeters.

By imaging, the spleen will be considered normal if <13 cm using craniocaudal measurement (Hallek M, 2018).

There is no international consensus on the size of a normal liver (Hallek M, 2018). For the purpose of this trial, a decrease to ≤ 18 cm in the longest diameter on CT scan will be considered a normal liver. The iwCLL 2018 criteria will be utilized to determine the response.

8.3.3 NON-TARGET LESIONS

Any other measurable and abnormal nodal lesions not selected for quantitation as target lesions may be considered non-target lesions. In addition, non-measurable evidence of CLL such as nodal lesions with both diameters < 1.0 cm, extra-nodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, and lesions with artifacts may be considered as non-target disease.

The presence or absence of non-target disease should be recorded at baseline and as per the study assessment schedule. If present at baseline, up to 6 non-target lesions should be recorded. The non- target disease at baseline will be used as a general reference to further characterize regression or progression of CLL during assessments of the objective tumor response during treatment. Measurements are not required and these lesions should be followed as "present" or "absent".

8.4 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Responses will be categorized as CR, PR, SD, or PD. Response criteria for this protocol will be per iwCLL 2018 criteria (see Appendix D). Response to therapy includes 2 groups of parameters that need to be documented. Group A assesses the lymphoid tumor load (CT) and constitutional symptoms; group B assesses the hematopoietic criteria. The hemataopoietic criteria will be evaluated using the lab testing on Cycle 4 Day 1 and Cycle 13 Day 1.

For the purpose of this study, the bone marrow biopsy response criterion will be calculated using the following formula:

Cellularity x % involvement of CLL= percent of response

If the reporting pathologist provides a range for B-cell or lymphocytic leukemia involvement (i.e.,80-85%), the higher number of the range will be used for the calculation.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until disease/recurrence progression (taking as a reference for disease progression the smallest measurements recorded since treatment started). Where imaging data are available, these data will supersede physical examination data in determining tumor status.

8.5 LYMPHOCYTOSIS DURING THERAPY

Upon initiation of umbralisib, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) may occur. The onset of isolated lymphocytosis usually occurs during the first few weeks of umbralisib therapy and usually resolves within three to four months. Patients with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression (i.e., disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy.[7]

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE

This is a phase 2 study designed to assess the overall response rate (CR + PR) and progression-free survival (PFS) of Umbralisib in treatment naïve patients with CLL. The primary endpoint is the overall response rate (ORR) from the time of treatment. The study will plan to enroll up to 40 subjects, and assuming 10% attrition, the study will have approximately 35 subjects remaining for analysis. Any subjects who are screen failures are not considered enrolled and may be replaced to meet the accrual goal. Enrollment is expected to be completed in approximately 18 months with 24 months follow up. The ORR for the standard of care is about 60%. We expect that Umbralisib treatment could lead to 80% ORR. A Simon 2-stage minimax design that differentiates ORRs of 0.60 (null hypothesis) and 0.80 (alternative hypothesis) will be used to assess treatment efficacy, with the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) both set at 0.10. Twenty seven patients will be accrued in the first stage of the study. If 18 or fewer patients have a response, then the study will be terminated and declared negative. If 19 or more patients have a response, then an additional 8 patients will be accrued to the second stage. At the conclusion of the study, if 25 or more patients have a response out of a total of 35 patients enrolled, the regimen will be considered worthy of further investigation.

9.2 GENERAL ANALYSIS CONVENTION

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.

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, maximum, and appropriate percentiles for continuous variables, and the number and percentage by category for categorical data. Summaries will be presented. The data listings will include all available efficacy and safety data.

9.3 STUDY POPULATIONS

Two study populations, intent-to-treat (ITT) and safety populations, are pre-defined for this study. The ITT population will include all enrolled patients who provide some efficacy assessments and the safety population will include all patients who take at least one dose of study medication. The efficacy analyses will be based on ITT population and the safety analyses will be based on the safety population.

9.4 PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics will be summarized as percentages for categorical variables and as mean, standard deviation, median, minimum and maximum for continuous measures. The analyses of baseline characteristics will be performed for the ITT population.

9.5 MEDICAL HISTORY

Medical history will be captured at the Screening visit.

9.6 EXTENT OF EXPOSURE

The dose (mg) of study drugs administered, the total number of doses of study drug, and the duration of treatment (number of study cycles) will be summarized with descriptive statistics. The number and percentage of patients whose dose is modified at any time will be summarized by each type of modification by cycle and overall. The proportion of patients completing each cycle of treatment will be summarized.

9.7 EFFICACY ANALYSES

Each patient will be assigned to one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data).

Many of the efficacy measures will be based on disease assessments. The best clinical response as well as disease progression will be determined by the treating investigator. Scans should be kept on file in cases where independent review or confirmation may be warranted. Definitive disease progression will be based on standard criteria (Hallek et al. 2018) 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.

During the study period, all patients will be evaluated for response by CT or MRI within 14 days prior to Cycle 4, Day 1 for Cycle 3 assessment, and within 14 days prior to Cycle 13, Day 1 for Cycle 12 assessment, and at any other time point to confirm progression. Patients who fail to achieve a partial or complete response to umbralisib at the Cycle 3 assessment will discontinue study treatment. At that time, patients- will be provided appropriate options to receive established frontline therapy. Patients who demonstrate a partial or complete response will be treated until disease progression, unacceptable toxicity, or the end of the study.

9.8 MISSING VALUE HANDLING PROCEDURES

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 may vary depending upon the parameter.

9.9 STATISTICAL ANALYSES

9.9.1 PRIMARY EFFICACY VARIABLE - PFS

The two primary efficacy outcomes are overall response rate (ORR) and progression-free survival (PFS). Time to progression event "Survival" curve will be presented using Kaplan-Meier method. Median time to event and the 95% confidence interval of the median times will be presented, if estimable. Median time to event will be tested against the null hypothesis value using a one-sample (one-sided) log-rank test.

PFS is defined as the interval from Cycle 1, Day 1 to the earlier of the first documentation of definitive disease progression or death from any cause.

Overall Response Rate (ORR) will be determined according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (Hallek et al. 2018).

We will estimate Overall Response Rate (ORR), which is defined as percent of patients who achieve CR or PR. We will also estimate exact 95% confidence intervals for the response rates. These will be followed by additional logistic regression analyses model to adjust for demographic and baseline parameters.

10 SAFETY REPORTING AND ANALYSIS

10.1 SAFETY ANALYSES

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 analyses will be performed using the safety population. Safety variables will be tabulated and presented by the dose of umbralisib study drug actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

10.2 ADVERSE EVENT CHARACTERISTICS

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. Expected AEs are defined as those described in the Umbralisib Investigator Brochure.

Definitions of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related

to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 is to be used for the grading of severity of symptoms and abnormal findings. For adverse events not covered by the NCI-CTCAE Version 4.0 grading system, the following definitions will be used:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

10.3 ADVERSE EVENTS (AES) AND TREATMENT EMERGENT ADVERSE EVENTS (TEAES)

All AEs and SAEs occurring on study will be listed by patient. Adverse events will be collected per the Moffitt SOP for adverse events, serious adverse events, and unanticipated problems. For the purpose of this trial, adverse event collection:

- Occurs after first dosing of study medication (Cycle 1, Day 1) and through the end of the study or up through 30 days after the last dose of study treatment, or
- Is considered treatment-related regardless of the start date of the event, or
- Is present before first dosing of study medication but worsens in intensity or the investigator subsequently considers treatment-related.

Adverse Events that are considered at least possibly related to study treatment will be tabulated as well as deaths, SAEs, and events resulting in treatment discontinuation.

10.4 ADVERSE EVENTS/SERIOUS ADVERSE EVENT CAUSALITY ASSESSMENT

The Investigator must also assess the relationship of any adverse event to the use of study drugs (whether none, one, or both), based on available information, using the following guidelines:

- **Not Related**: Clear-cut temporal and/or mechanistic relation to a cause other than the study drug(s).
- **Doubtful**: There is no reasonable possibility that the event is related to the study drug(s) but a definite cause cannot be ascertained.
- **Possible**: There is still a reasonable possibility that the cause of the event was the study drug(s) but there exists a more likely cause of the event such as complications of progressive disease.
- **Probable**: The most likely cause of the event is the study drug(s) but other causes cannot be completely excluded.
- **Definite:** Clear cut temporal and/or mechanistic relation to the study drug(s). All other

causes have been eliminated. Events classified as definite will often be confirmed by documenting resolution on discontinuation of the study drug and recurrence upon resumption.

10.4.1 RECORDING OF ADVERSE EVENTS

All adverse events of any patient during the course of the study will be recorded in the Moffitt On Core electronic database. The investigator will give his or her opinion as to the relationship of the adverse event to study drug treatment (i.e., whether the event is related or unrelated to study drug administration – umbralisib). If the adverse event is serious, it should be reported as described in Sections 10.5.2 and 10.6. Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs regardless of seriousness or relationship to umbralisib treatment spanning from Cycle 1, Day 1 until 30 calendar days (+/-7 days) after discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded.

10.4.1 ABNORMAL LABORATORY VALUES AND VITAL SIGNS

The reporting of abnormalities of vital signs as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE is fulfilled, the vital signs abnormalities cause the patient to discontinue study treatment, or the investigator insists that the abnormality should be reported as an AE. Abnormal laboratory results should be recorded as an adverse event if they are associated with an overdose, require or prolong inpatient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be recorded as an AE, and the associated laboratory value or vital sign should be considered additional information to record related to the AE. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

Clinical Laboratory Results will be summarized. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Patients with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized and graded per NCI CTCAE Version 5.0 when applicable. Patient incidence of abnormal laboratory results will be summarized by treatment group and maximum grade for each abnormal laboratory finding.

10.4.2 HANDLING OF ADVERSE EVENTS

All adverse events resulting in discontinuation from the study should be followed until resolution or stabilization. Patients should be followed for AEs for 30 calendar days (+/-7 days) after

discontinuation or completion of protocol-specific treatment (umbralisib). All new AEs occurring during this period must be recorded and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record]. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

10.5 SERIOUS ADVERSE EVENTS

10.5.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS

The definitions of serious adverse events (SAEs) are given below. The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that:

- results in death, is immediately life-threatening,
- requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- causes a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life- threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per iwCLL Hallek et al. 2018), should not be reported as a serious adverse event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE that is suspected to be at least possibly related to study medication and is an unexpected event. SUSAR reporting is encompassed within SAE reporting guidelines as defined in this section.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility

- Hospice or skilled nursing facility, Nursing homes, Custodial care or Respite care facility
- Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as a serious adverse event.

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs and SAEs.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to TG Therapeutics in order to comply with regulatory requirements. Serious adverse events may occur at any time from signing of the consent form through the 30-day follow-up period after the last study treatment. TG Therapeutics should be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel. Report SAEs to TG Therapeutics at safety@tgtxinc.com (copy gabriel.green-lemons@tgtxinc.com and donna.gesumaria@tgtxinc.com on an SAE Form (MedWatch FORM FDA 3500 or equivalent). Include the TG Therapeutics, Inc. tracking number (TGR-NTG-006) on the SAE report .SAEs are to be followed until resolution (with autopsy report, if applicable).

CLL progression or death due to CLL progression should be reported by the investigator as a serious adverse event only if it is assessed that umbralisib caused or contributed to the CLL progression (i.e. by a means other than lack of effect).

The investigator must review and sign off on the SAE data on the SAE report.

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to TG Therapeutics as soon as it is available; these reports should be submitted using the appropriate SAE form.

10.6 SAE REPORTING REQUIREMENTS BY INVESTIGATOR TO FDA AND IRB

The investigator is responsible for reporting SAEs to the FDA in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

The investigator is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the FDA within 7 calendar days of the first knowledge of the event by the treating physician or research personnel. The investigator will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs (SUSAR) associated with the use of the study medications to the FDA by a written safety report within 15 calendar days of the first knowledge of the event by the treating physician or research personnel.

Investigators must report SAEs, SUSARs and follow-up information to their responsible Institutional Review Board (IRBs)/Independent Ethics Committee according to the policies of the responsible IRB (Research Ethics Committee).

10.7 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and within medical records. Avoid colloquialisms and abbreviations. All AEs, including those that meet SAE reporting criteria, should be recorded; AEs that meet the definition of an SAE should additionally be reported.

10.8 DIAGNOSIS VS. SIGNS AND SYMPTOMS

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. 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 as an AE or SAE as appropriate on the relevant form(s). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

10.8.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or as an AE. If a persistent AE becomes more severe (changes from a Grade 1 or 2 AE to a Grade 3 or 4 AE) or lessens in severity (changes from a Grade 3 or 4 AE to a Grade 1 or 2 AE), it should be recorded on a separate SAE Report Form and/or as a separate AE.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or as an AE for each recurrence.

10.8.2 ABNORMAL LABORATORY VALUES

Abnormal laboratory results should be recorded as an adverse event if they are associated with an overdose, require or prolong inpatient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information to record related to the AE. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or as an AE.

10.8.3 DEATHS

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of the patient's CLL for up to 30 days post the last dose of study drug will be recorded, but are exempted from expedited reporting. All other on-study

deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported as described in Sections 10.5.2 and 10.6.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS".

10.8.4 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in hospital admission of > 24 hours or prolongs hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. See section 10.5.1.

10.8.5 PRE-EXISTING MEDICAL CONDITIONS

A pre-existing relevant medical condition is one that is present at the start of the study. Such conditions should be recorded in the subject's medical history. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the appropriate SAE Report Form and/or as an AE, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

10.8.6 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

The following are events of special interest, and will need to be reported expeditiously:

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

During the course of the study, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix A- Contraceptive Guidelines and Pregnancy) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

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

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must notify the Study Chair and TG Therapeutics as soon as possible.

If a patient becomes pregnant while enrolled in the study , , submit a Pregnancy Report Form to TG Therapeutics, Inc. within 24 hours of the first knowledge of the event by the investigator or research personnel following the same process described for reporting SAEs to TG Therapeutics, Inc. Include the TG Therapeutics, Inc. tracking number (TGR-NTG-006) on the Pregnancy Report Form and include an assessment of the causal relationship to the study drug. Male subjects must

contact the investigator immediately if their female partner becomes pregnant, and the investigator must submit a Pregnancy Report Form to TG Therapeutics, Inc. within 24 hours as described above. Consent should be obtained from the pregnant female subject/male subject's partner to allow the pregnancy to be followed up for the full duration of the pregnancy (or until spontaneous abortion or voluntary termination), to collect the outcome with details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, as applicable. Additionally, medical information should be collected on the newborn for 6 months after birth, as permitted by local regulations.

Any SAE experienced during pregnancy must be reported to TG Therapeutics, Inc. SAEs experienced during pregnancy must be reported to TG Therapeutics, Inc. on the SAE Report Form within 24 hours of the first knowledge of the event by the investigator or research personnel following the same process as described above for SAEs. Abortions (spontaneous, accidental, or therapeutic) must also be reported to TG Therapeutics.

Study Drug Overdose

Symptomatic and non-symptomatic overdose must be recorded. Any accidental or intentional overdose with the study treatment (umbralisib) that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to TG Therapeutics immediately (within 24 hours) using the corresponding SAE form, and following the same process described for SAEs. If a study drug overdose occurs, patients should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

Secondary / Second Primary Malignancy

Any secondary malignancy event must be reported via the SAE form as previously described (in addition to the routine AE reporting mechanisms). Any malignancy possibly related to cancer treatment should also be reported via the routine reporting mechanisms outlined in the protocol.

11 CLINICAL DATA COLLECTION AND MONITORING

11.1 AMENDMENTS TO THE PROTOCOL

Proposed amendments to the protocol require review and approval by TG Therapeutics prior to implementation. After approval by TG Therapeutics, the amendment will be submitted formally to the FDA by the Principal Investigator. The protocol amendment must also be reviewed and approved by the institutional IRB prior to implementation. If an amendment to the protocol substantially alters the study design or the potential risks to patients, patients' consent to continue participation in the study should be obtained per institutional policies.

11.2 DATA OWNERSHIP AND PUBLICATION

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. By conducting this study, the

Investigator affirms to TG Therapeutics that he or she will maintain, in strict confidence, information furnished by TG Therapeutics, except as exempted for regulatory purposes.

All manuscripts, abstracts, or other presentation materials generated by site investigators must be reviewed and approved by TG Therapeutics prior to submission.

11.3 STUDY RECORDS RETENTION

Study records will be retained for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

11.4 CLINICAL MONITORING

Data will be captured in OnCore, Moffitt's electronic Clinical Trials Database. For each participant enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those patients who fail to complete the study. If a patient stops dosing or terminates from the study, the dates and reasons must be noted on the CRF. If a patient terminates from the study because of a dose limiting toxicity, thorough efforts should be made to clearly document the outcome. Regulatory documents and case reports forms will be monitored internally according to the Moffitt Cancer Center monitoring policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification on data entry, validation of appropriate consent process, reporting on SAEs, and adherence of the protocol, GCP guidelines and applicable regulatory requirements.

11.5 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the OnCore data entry system and QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the staff for clarification/resolution.

Following written SOPs, the Moffitt internal monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., good laboratory practices (GLP), good manufacturing practices (GMP).

The investigational site will provide direct access to source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

All staff will be trained by the PI through a site initiation presentation which may be performed by a power point training or a summary document for training on the initial protocol. This will be provided to those staff unable to attend the initiation presentation . Training will be performed by self-study for approved amendments and documented per the Moffitt CTO SOP . Documentation of training will befiled in the electronic regulatory binder.

11.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, of MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the study staff to identify and report deviations as defined by the Moffitt Clinical Trials Office standard. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

12 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

12.1 IRB APPROVAL

The study protocol, ICF, and other necessary study documents must be submitted to the IRB for ethical review and approval prior to the study start. Principal Investigator is also responsible for insuring IRB renewals, and IRB approval for all subsequent protocol amendments and changes to the informed consent document.

12.2 INFORMED CONSENT

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator or his designee to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study must be obtained.

12.3 CONFIDENTIALITY

Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws. HIPAA regulations require that, in order to participate in the study, the patient should be informed of following:

- What protected health information (PHI) will be collected from patients in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of TG Therapeutics, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data. Patients will be informed of their rights within the ICF.

12 REFERENCES

1. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. *New England Journal of Medicine*;0(0):null.

2. Barr PM, Brown JR, Hillmen P, et al. Dose adherence and baseline exposure analysis of the ibrutinib 420 mg dose administered to patients with previously treated chronic lymphocytic leukemia (CLL). ASCO Annual Meeting Proceedings; 2015:7012.

3. Friedman DR, Simms T, Allgood SD, et al. The PI3K-δ inhibitor TGR-1202 induces cytotoxicity and inhibits phosphorylation of AKT in 17p deleted and non-17p deleted CLL cells in vitro. *Cancer Research*. 2014;74(19 Supplement):4518-4518.

4. Burris HA, Patel MR, Brander DM, et al. TGR-1202, a novel once daily pi3k δ inhibitor, demonstrates clinical activity with a favorable safety profile, lacking hepatotoxicity, in patients with chronic lymphocytic leukemia and B-cell lymphoma. *Blood*. 2014;124(21):1984-1984.

5. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. *New England Journal of Medicine*. 2014.

6. 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(12):5446-5456.

7. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *Journal of Clinical Oncology*;30(23):2820-2822.

8. Hallek, M., et al., Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. Blood, 2018. Jun 21;131(25):2745- 2760. doi: 10.1182/blood-2017-09-806398. Epub 2018 Mar 14.

12 APPENDIX A- CONTRACEPTIVE GUIDELINES AND PREGNANCY

Women Not of Childbearing Potential are Defined as Follows:

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Contraceptive Guidelines for Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 30 days after stopping treatment. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomised male partner should be the sole partner for that patient.
4. Oral contraception, injected or implanted hormonal methods.
5. Use of a combination of any two of the following (a+b):
    a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Women of child-bearing potential must have a negative serum or urine pregnancy test ≤ 3 days prior to initiating treatment.

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring, must use condoms during treatment and for 30 days after discontinuation of the study drug. They should not father a child in this period.

Pregnancies

To ensure patient safety, each pregnancy, either in a female patient or the female partner of a male patient on study treatment, must be reported to TG Therapeutics Inc. within 24 hours of learning of its occurrence. The pregnancy must be followed until term. Both the mother and the infant child must be followed for 6 months after termination of pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug and reported by the investigator to TG Therapeutics Inc. Any SAE experienced during pregnancy must be reported to TG Therapeutics Inc.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

15 APPENDIX B – NYHA CLASSIFICATIONS

New York Heart Association (NYHA) Classifications

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.

III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

16 APPENDIX C – HEPATITIS B SEROLOGIC TEST RESULTS

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis

17 APPENDIX D – IWCLL RESPONSE CRITERIA VERSION 2018

GROUP	PARAMETER	CR	PR	PD	SD
A	Lymph nodes	None ≥ 1,5 cm	Decrease ≥ 50% (from baseline) [1)]	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size*	Spleen size < 13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline	Change of -49% to +49%
B	Platelet count	≥ 100.000/µl	≥ 100.000/µl or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49 to +49%
	Hemoglobin	≥ 11,0 g/dl (untransfused and without erythropoietin)	≥ 11 g/dl or increase ≥ 50% over baseline	Decrease of ≥ 2 g/dl from baseline secondary to CLL	Increase < 11,0 g/dl or < 50% over baseline, or decrease < 2 g/dl
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules.	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

1) Sum of the products of 6 or less lymph nodes (as evaluated by CT scans and physical exam in clinical trials, or by physical exam in general practice).

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

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