Official Title:	**A Phase II Study Evaluating the Safety and Efficacy of Umbralisib (TGR-1202) in Combination with Ublituximab in Patients with Treatment Naïve Follicular Lymphoma and Small Lymphocytic Lymphoma**
NCT Number:	NCT03828448
Document Date:	Protocol Version 2.0: 20 December 2018

Protocol version/Date: Version 2.0 / 20 DEC 2018

Protocol #: UTX-TGR-203

TITLE: A Phase II Study Evaluating the Safety and Efficacy of Umbralisib (TGR-1202) in Combination with Ublituximab in Patients with Treatment Naïve Follicular Lymphoma and Small Lymphocytic Lymphoma

Sponsor: TG Therapeutics, Inc.
2 Gansevoort Street, 9th Floor
New York, NY 10014
Tel: (212) 554-4484

IND Number: 114,779

Study Chair: [redacted], M.D., Ph.D.
[redacted]

Medical Monitor: [redacted], MD
Tel: [redacted] ext. [redacted]

Study Coordination: TG Therapeutics, Inc.
2 Gansevoort Street, 9th Floor
New York, NY 10014
Tel: (212) 554-4484

Version: 1.0 **Date:** 24 March 2018
Version: 1.1 **Date:** 26 April 2018
Version: 2.0 **Date:** 20 December 2018

PROTOCOL ACCEPTANCE FORM

Protocol Title:	**A Phase II Study Evaluating the Safety and Efficacy of Umbralisib (TGR-1202) in Combination with Ublituximab in Patients with Treatment Naïve Follicular Lymphoma and Small Lymphocytic Lymphoma**
Protocol Number:	UTX-TGR-203
IND Number:	114,779
Date FINAL:	20 December 2018

I have read the attached protocol and agree that it contains all the necessary details for performing UTX-TGR-203.

I will provide copies of the protocol and of the ublituximab and umbralisib Investigator's Brochures, which were given to me by TG Therapeutics (Sponsor), to all members of the study team for whom I am responsible and who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding ublituximab, umbralisib, and the conduct of the study.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining the prior approval of TG Therapeutics and of the IRB. I will submit the protocol modifications and/or any informed consent modifications to TG Therapeutics and the IRB, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964) including all amendments up to and including the Washington Clarification (2002).

Print Name	Signature	Date

TABLE OF CONTENTS

SUMMARY OF CHANGES

Version 1.1 (Dated 26 April 2018) of this Protocol is the first amendment to this clinical trial and contains the following modifications:

- T-cell Lymphocyte Subsets will be analyzed by the Sponsor designated central laboratory instead of the site's local laboratory (Section 5.1.2.1)
- Updated guidance for prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy (Section 6.2.1)

Version 2.0 (Dated 20 December 2018) of this Protocol is the second amendment to this clinical trial and contains the following modifications:

- The term "patient" was replased with "subject" throughout;
- Administrative and editorial changes;
- Two safety run-in cohorts of 3 - 6 subjects each were added at a dose of 600 mg and 800 mg umbralisib to evaluate for key immune mediated toxicities. In the absense of unacceptable toxicity, enrollment will proceed with all subjects receiving 800 mg umbralisib.
- Inclusion Criteria
    - Subjects are now required to have a need for systemic therapy prior to enrollment;
    - Statement added to bilirubin noting exception of Gilbert's Disease and Autoimmune Hemolytic Anemia;
    - Calculated Creatinine Clearance utilizing the Modified Cockroft-Gault Formula and IBM;
- Exclusion Criteria
    - The exclusion of prior cancer therapy was clarified to prior "systemic" cancer therapy;
    - Updated exclusionary criteria for hepatitis and CMV screening criteria for clarity;
    - Updated reference to note appendix F not D;
    - Added parameters for corticosteroids during screening;
- Schedule of Assessments and Treatment (Section 5.0)
    - Update response assessment criteria. Clarified assessments should be within 14 days of Day 1 of Cycles 3, 6, and 12, and then every 6 months until cycle 24. After cycle 24, response assessments should occur at least every 12 months.
- Clarified pre-medications for ublituximab throughout protocol.
- Updated PJP/Antiviral prophylaxis drug recommendations.
- Language in protocol removed requiremment of subject to discontinue protocol therapy if drug is held greater than 28 days for recovery. Current languauge states to notify TG Therapeutics if study drug (s) are re-initiated after being held for greater than 2 cycles.
- Dose Modification Table
    - Addition of liver dose modifications based on grade.
    - To respiratory/infection added statement for sinopulmonary infections clearly not related to immune-mediated pneumonits, TGR-1202 (umbralisib) may be continued at investigator discretion.

STUDY SYNOPSIS

Protocol no.	UTX-TGR-203
Study Title	A Phase II Study Evaluating the Safety and Efficacy of Umbralisib (TGR-1202) in Combination with Ublituximab in Patients with Treatment Naïve Follicular Lymphoma and Small Lymphocytic Lymphoma
Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
IND #	**Umbralisib:** 116,762 **Ublituximab:** 114,779
Study Chair	[redacted] M.D., Ph.D. [redacted]
Study Sites & Enrollment	• Up to 15 trial sites may participate in this study. • Duration of the study is approximately 36 months. • Up to 50 subjects are expected to be enrolled in this study.
Study Rationale	Treatment for newly diagnosed FL and SLL routinely includes chemotherapy based combinations, usually with a monoclonal antibody (Rituxan + bendamustine). These chemotherapy-based regimens combined with monoclonal antibodies lead to heterogenous clinical outcomes with many subjects experiencing relapse and/or unfavorable toxicities, especially elderly subjects. New, novel treatments are needed which can be used in combination with monoclonal antibodies that are chemotherapy-sparing with convenience of oral daily dosing. This trial will evaluate umbralisib + ublituximab in treatment naïve FL and SLL subjects. Umbralisib (also referred to as TGR-1202) 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 been safely administered in subjects with various hematologic malignancies at doses up to and including 1200 mg QD. Ublituximab (TG-1101) is a glycoengineered monoclonal antibody that binds to the trans-membrane antigen CD20 found on B-lymphocytes. The binding of ublituximab induces an immune response that causes lysis of B cells. A Phase I study evaluating the ublituximab + umbralisib (U2) regimen in subjects with relapsed or refractory FL or SLL showed a favorable safety profile and response rate (Lunning, et. al. ASCO 2015). A Phase 2 study in subjects with relapsed or refractory indolent lymphomas is ongoing with umbralisib montherapy as well as the U2 regimen. A Phase 3, randomized study (UTX-TGR-304) to assess efficacy and safety of ublituximab + umbralisib compared to obinutuzumab + chlorambucil in subjects with treatment naïve and relapsed/refractory CLL is currently ongoing with no observed safety trends reported (DSMB Sep 2018). To date, umbralisib and ublituximab either as single agents or in combination have been administered to over 1000 subjects worldwide.

Study Objectives	**PRIMARY OBJECTIVE** • To assess the overall response rate (ORR) in subjects with treatment naïve follicular lymphoma (FL) and small lymphocytic lymphoma (SLL) treated with umbralisib in combination with ublituximab. **SECONDARY OBJECTIVES** • To evaluate the safety of umbralisib in combination with ublituximab. • To assess the duration of response (DOR), Complete Response (CR) and progression-free survival (PFS) in subjects with treatment naïve FL and SLL treated with umbralisib + ublituximab. [redacted]
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Treatment naïve, histologically-confirmed diagnosis of Follicular Lymphoma (FL) Grade 1, 2, or 3a, or Small Lymphocytic Lymphoma (SLL). 2. Subjects must have measurable or evaluable disease, and must have documented evidence for requiring treatment (bulky disease (>5 cm), high LDH, B symptoms, threatened organ function, splenomegaly, cytopenias due to lymphoma, or effusions). 3. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) ≥ 0.75 x 10^9/L. **Note:** No growth factors or transfusions are allowed to meet eligibility criteria. b. Platelets ≥ 50 x 10^9/L. **Note:** No growth factors or transfusions are allowed to meet eligibility criteria. c. Total bilirubin ≤1.5 times the upper limit of normal (ULN) with the exception of Gilbert's Disease and Autoimmune Hemolytic Anemia. d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement e. Creatinine ≤ 2.0 mg/dL OR calculated creatinine clearance (as calculated by the modified Cockcroft-Gault formula using ideal body mass [IBM] instead of mass) ≥ 30 mL/min 4. ECOG performance status ≤ 1. 5. Patients must be ≥18 years of age. 6. Ability to swallow and retain oral medication 7. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of either study drug.

	8. Willingness and ability to comply with trial and follow-up procedures.
Exclusion Criteria	Subjects who meet any of the following exclusion criteria are not to be enrolled to this study: 1. Subjects currently receiving systemic cancer therapy or previously systemic received cancer therapy for their lymphoma (i.e., chemotherapy, immunotherapy, biologic therapy, hormonal therapy, surgery, transplant, and/or tumor embolization). 2. Evidence of chronic active Hepatitis B defined as Hepatitis B surface antigen positive or Hepatitis B DNA positive by PCR (HBV, NOT including subjects with prior hepatitis B vaccination who are Hepatitis B surface antibody positive only;) or chronic active Hepatitis C infection (HCV) defined as Hepatitis C RNA positive by PCR, cytomegalovirus (CMV) DNA positive by PCR, or known history of HIV. If HBc antibody, HCV antibody or CMV IgG and/or IgM antibody is positive, subjects must be evaluated for the presence of HBV, HCV, or CMV by PCR - See Appendix F. 3. Subject has received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to Cycle 1/Day 1 or has not recovered from side effects of such therapy. 4. Primary central nervous system lymphoma (PCNSL) or known intracranial involvement, or leptomeningeal metastases. 5. Ongoing immunosuppressive therapy including systemic corticosteroids. Subjects are allowed to use topical or inhaled corticosteroids. a. Corticosteroid therapy started at least 7 days prior to Cycle 1/Day 1 (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. 6. Known history of drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, or cirrhosis of the liver. 7. 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 (New York Heart Association functional classification III-IV)[see Appendix C- NYHA Classifications] b. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or 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. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting within 6 months of enrollment. 8. Malignancy other than Follicluar Lymphoma or SLL within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of Cycle 1/Day 1. 9. Women who are pregnant or lactating.
Study Design	This is a Phase 2 open-label study of umbralisib in combination with ublituximab administered to subjects with treatment naïve follicular lymphoma (FL) and small lymphocytic lymphoma (SLL). Daily doses of oral umbralisib will be administered for 24 cycles in the absence of disease progression, unacceptable toxicity, or withdrawal from treatment. Two safety run-in cohorts of 3 - 6 subjects each at a dose of 600 mg and 800 mg umbralisib will first be enrolled to evaluate for key immune mediated toxicities. In the absense of unacceptable toxicity, enrollment will proceed with all subjects receiving 800 mg umbralisib. A fixed dose of 900 mg of ublituximab will be administered on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycles 2-6, Cycle 9 and 12. Treatment cycles are 28 days. PET scans **must** be done at screening, within 14 days of Cycle 6 Day 1, and to confirm CR (if applicable). During the study period, all subjects will be evaluated for response by CT (if contrast CT is contraindicated MRI with a non-contrast CT Chest should be completed) within 14 days of Day 1 of Cycles 3, 6, and 12. After Cycle 12, subjects should be evaluated for response by CT (if contrast CT is contraindicated MRI with a non-contrast CT should be completed) approximately every 6 cycles unless clinically indicated sooner (at the discretion of the treating physician). After 24 cycles (approximately 24 months) of treatment, subjects will discontinue study medication and be followed for progression-free survival. Subjects should continue to be followed for PFS at least every 12 months or more frequently if medically necessary. Sites should utilize a consistent method for response evaluations throughout study. Up to 50 subjects are expected to be enrolled in this study.

Statistics	This is an open-label Phase 2 study of umbralisib in combination with ublituximab. This study is designed to evaluate the overall response rate (CR+PR), as well as duration of response (DOR), complete response (CR) and progression-free survival (PFS) in treatment naïve follicular lymphoma and small lymphocytic lymphoma subjects. Assessment of lymphoma response (CR, PR, or SD) and disease progression will be evaluated as outlined in the schedule of assessments, per the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007). Safety will be examined on an ongoing basis while the study is being conducted. Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE).
[redacted]	[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and Definitions of Terms	
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
AUC0-t	Area under the plasma-concentration time curve from zero up to the last measureable concentration
AUClast	Area under the concentration time curve at last dose
BM	Bone marrow
BSA	Body surface area
Ca	Calcium
CBC	Complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHF	Congestive heart failure
Cmax	Peak drug concentration
CMP	Comprehensive metabolic profile
CR	Complete Response
CRF	Case Report Form
CSF	Colony-stimulating factor
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HTRF	Homogenous time resolved fluorescence assay
IB	Investigators Brochure
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
MUGA	Multigated (Radionuclide) angiogram
N/A	Not applicable
NCI	National Cancer Institute
N/D	Not done
NOAEL	No observed adverse effect level

NYHA	New York Heart Association
PCNSL	Primary central nervous system lymphoma
PD	Pharmacodynamic
PDKI	3-Phosphoinositide-dependent protein kinase-1
PFS	Progression-Free Survival
P53	Tumor protein 53
P-gp	P-glycoprotein
PHI	Protected health information
PI3K	Phosphoinositide-3-kinase
PK	Pharmacokinetic
PR	Partial Response
PTEN	Phosphatase and tensin homolog
QA	Quality assurance
RP2D	Recommended phase II dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SLL	Small Lymphocytic Lymphoma
T1/2	Terminal half-life
TKI	Tyrosine Kinase Inhibitor
tmax	Time of maximum observed concentration
TTP	Time to tumor progression
WHO	World Health Organization

1 INTRODUCTION

1.1 INDOLENT NON-HODGKIN'S LYMPHOMA

In the US, an estimated 72,000 new cases of Non-Hodgkin's Lymphoma (NHL) were reported in 2015. Deaths, due to the disease, totaled approximately 20,000, according to the American Cancer Society (American Cancer Society, 2015). Indolent Non-Hodgkin's Lymphoma (iNHL) makes up about 30% of all NHL cases in the United States, and subtypes include:

- Follicular lymphoma (FL)
- Waldenström macroglobulinemia (WM)
- Marginal zone lymphoma (MZL)
- Small cell lymphocytic lymphoma (SLL)

Follicular lymphoma (FL) and Small Lymphocytic Lymphoma (SLL) together represent most of the subjects in the iNHL subtype. Treatment for newly diagnosed FL and SLL ranges from a watch-and-wait approach to a more aggressive therapy including chemotherapy based combinations, usually with a monoclonal antibody (Rituxan + Bendamustine or other chemo based regimens). Although effective, these chemotherapy- based regimens will often lead to relapse and unfavorable toxicities, especially for elderly subjects.

1.2 UMBRALISIB (TGR-1202)

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. The PI3Ks are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies.

In the Phase I study, to-date, a total of 81 subjects have been treated with umbralisib, including 22 FL and 21 CLL subjects. In all treated subjects, the most commonly-occurring (≥18% subjects) adverse events (AEs; all grades, all causality) were nausea, diarrhea, fatigue, rash, headache, cough and vomiting, the majority of which were Grade 1/2. The only Grade ≥3 AE occurring in < 5% of subjects was anemia (9%). Discontinuation due to an adverse event with TGR-1202 was reported in 6/81 (7%) of subjects. Of the 17 evaluable CLL subjects, 16 (94%) achieved a nodal PR of which 10 (59%) achieved a PR per Hallek 2008 criteria. Clinical activity was also observed in FL, with 12/16 (75%) evaluable subjects experiencing tumor reductions, and a preliminary 38% ORR (6/16) with an additional 2 subjects achieving 49% reductions in tumor burdens (subjects continuing to receive ongoing therapy). The longest period of treatment on the study to-date is 34 cycles (over 2.5 years), and 27% of subjects have received more than 12 cycles of treatment. The Phase I study is closed as umbralisib is now in Phase 3 development for subjects with CLL (UNITY-CLL study).

1.2.1 PRE-CLINICAL EVALUATIONS OF UMBRALISIB

The potency of umbralisib against the human and mouse δ isoform of PI3K was evaluated in a homogeneous time resolved fluorescence (HTRF) based enzyme assay in the presence of ATP at

its Km value (100 µM) (Umbralisib Investigator Brochure). Selectivity over the other three isoforms, namely, α, β, and γ was also determined ([redacted], 2011; [redacted], 2011a, 2011b).

Data demonstrated the specificity of umbralisib towards PI3Kδ with >1000, 50 and 48-fold selectivity over α, β, and γ, respectively in an enzyme based assay, indicating that the primary mode of action of this compound is via inhibition of the δ isoform.

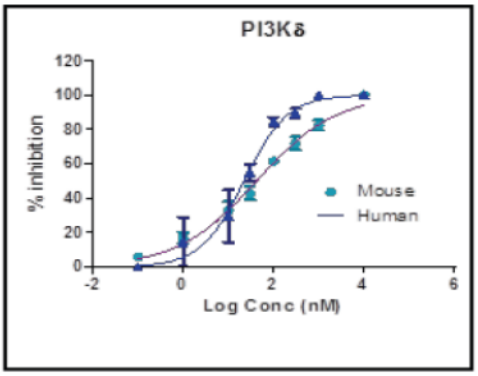


FIGURE 1: UMBRALISIB POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

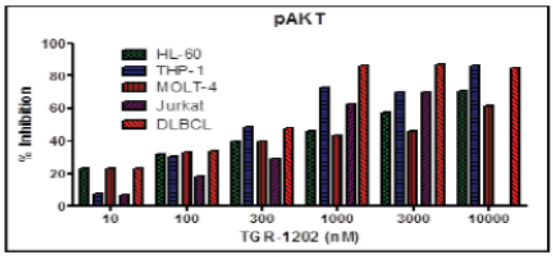
PI3K isoforms (Human)	IC_{50} (nM)
A	>10,000
B	1,116
Γ	1,065
Δ	22.23

Proliferation of immortalized leukemic cells representative of various indications was determined by a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay (Umbralisib Investigator Brochure). Cells were incubated with umbralisib for different time-periods (72 -96 h) based on their doubling time. Data demonstrated the ability of umbralisib to inhibit leukemic cell proliferation albeit with different potencies based on the cell type.

Overall, a 50% growth inhibition for majority of B, T, and monocytic cell lines was achieved at a concentration between 0.5 -7.5 µM of umbralisib.

Subsequent to cell viability, the effect of umbralisib on AKT phosphorylation (Umbralisib Investigator Brochure) was determined. AKT, a serine threonine kinase mediates the downstream effects of PI3K activity and modulates several cell processes including survival and growth. Reduction of phosphorylated AKT by umbralisib in representative cell lines was determined by Western blotting using a phospho-AKT (Ser473) antibody.

FIGURE 2: REDUCTION OF PAKT BY UMBRALISIB IN CELL LINES BY WESTERN BLOTTING

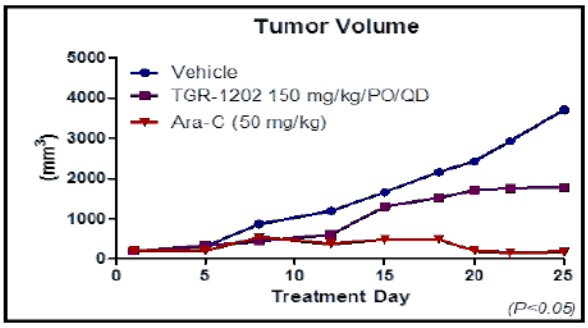


1.2.1.1 IN VIVO ACTIVITY

In vivo efficacy of umbralisib was confirmed in a subcutaneous mouse MOLT-4 xenograft model.

Oral administration of 150 mg/kg/QD over a 25-day period resulted in a significant delay in tumor growth.

FIGURE 3: UMBRALISIB IN VIVO EFFICACY



1.2.1.2 TOXICOLOGY

To assess the safety and toxicity of umbralisib a 28-day repeat dose study with a 14-day recovery period was conducted in CD-1 mice and beagle dogs, to evaluate the potential reversibility of findings and to support the use in humans. Umbralisib was administered orally in order to mimic the planned mode of clinical administration.

Once daily oral administration of umbralisib was tolerated in mice at free base dose levels of 50 and 150 mg/kg/day. Increases in liver weights, microscopic findings in the liver and the increases in serum cholesterol, and female only ALT, AST, and GGT levels were observed at 750 mg/kg/day of free base (the highest dose tested) and were considered adverse. The no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg/day in mice.

Once daily oral administration by capsule of umbralisib was well tolerated in dogs at levels of 50 and 150 mg/kg/day. The gastrointestinal tract, based on clinical signs, was the target organ system. Based on effects on body weight and the incidence and severity of emesis and diarrhea, the NOAEL was considered to be 150 mg/kg/day (114.5 mg/kg/day as free base) in this species.

Refer to the Umbralisib Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

1.2.2 CLINICAL DEVELOPMENT OF UMBRALISIB

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

Umbralisib is under evaluation in a single-agent Phase I dose-escalation study in subjects with relapsed and refractory hematologic malignancies (Burris et al, 2015). A total of 81 subjects were enrolled and eligible for safety evaluation, with 63 subjects evaluable for efficacy. The median age was 65 years (range 22-85) and 53% were male. Among all subjects the median number of prior therapies was 3 (with a range of 1-14), with 80% receiving prior rituximab-based chemotherapy. Histological diagnoses were as follows: FL (n=22), CLL (n=21), diffuse large B-cell lymphoma (DLBCL; n=14), Hodgkin's lymphoma (HL; n=9), mantle cell lymphoma (MCL; n=6), MZL (n=5), WM (n=2) and one each of hairy-cell leukemia (HCL) and T-cell lymphoma. The majority of subjects had an ECOG of 1 and 40/81 (49%) were refractory to prior therapy.

Subjects have been 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 . This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1200 mg QD, with no maximum tolerated dose (MTD) reached. Intra-subject dose escalation rules have allowed subjects enrolled into the study in early cohorts to increase their dose of umbralisib as subsequent higher cohorts have cleared safety evaluation.

A dose-dependent response has been observed with umbralisib, with a dose of 800 mg or higher of the initial formulation or any dose of the micronized formulation producing significant nodal reductions among CLL subjects. Of the 17 evaluable CLL subjects treated at or above this therapeutic threshold, 16/17 (94%) have achieved a nodal partial response, and nodal reductions show an improvement with time on umbralisib with a median time on study of 6 months. Clinical activity was also observed in FL, with 12/16 (75%) evaluable subjects experiencing tumor reductions, and a preliminary 38% ORR (6/16) with an additional 2 subjects achieving 49% reductions in tumor burdens (subjects continuing to receive ongoing therapy).

In all treated subjects (81), the most commonly-occurring (≥18% subjects) adverse events (AEs; all grades, all causality) were nausea, diarrhea, fatigue, rash, headache, cough and vomiting, the majority of which were Grade 1/2. The only Grade ≥3 AE occurring in >10% of subjects was neutropenia (11%). No events of colitis have been observed. Discontinuation due to an AE was reported in only 6/81 (7%) of subjects. Less commonly-occurring AEs (9-12%) included constipation, decreased appetite, hypokalemia, anemia, dizziness, dyspnea, pyrexia, abdominal pain, arthralgia and insomnia.

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.

Overall, umbralisib was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts with 800 mg QD selected as the Phase 2 dose in subjects with previously treated CLL and NHL.

1.2.2.2 HEALTHY SUBJECT PHARMACOKINETIC STUDIES

In parallel with the Phase 1 single-arm, dose-escalation study in subjects with relapsed or refractory hematologic malignancies; two healthy subject, crossover, bioequivalence pharmacokinetics studies have been completed. The first pharmacokinetic study was a Phase 1 drug-food interaction study with a single 200 mg oral dose of umbralisib in healthy volunteers followed by a second single dose Phase 1 pharmacokinetic study evaluating the absorption, distribution, metabolism and excretion characteristics of two different oral formulations of 200 mg umbralisib (original formulation vs. micronized formulation) in healthy volunteers.

1.2.2.2.1 TGR-1202-PK101: FOOD EFFECT

Study TGR-1202-PK 101 was two-period, randomized, two-way crossover, drug-food, drug-gender interaction study in 24 healthy subjects (12 males and 12 females) to assess the mean plasma umbralisib concentration over time following a single oral dose of 200 mg of umbralisib

under fasting and fed condition using the original formulation. In general, administration of umbralisib under fed conditions results in a higher rate of exposure relative to when the product was given under fasting conditions.

The statistical comparisons of umbralisib pharmacokinetic parameters under fasted and fed condition are shown below.

Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Fasting	Fed		
AUC_{0-t} (ng·hr/mL)	6029.87	9692.02	160.73	140.25 – 184.21
AUC_{0-inf} (ng·hr/mL)	8391.35	14047.17	167.40	141.59 – 197.92
C_{max} (ng/mL)	176.78	483.15	273.31	234.04 – 319.17

Food increased both the extent and rate of exposure of umbralisib. The extent (AUC_{0-t}) and total extent (AUC_{0-inf}) of exposure increased by 61% and 67%, respectively, when umbralisib was administered under fed conditions compared to fasting conditions. The peak plasma levels of umbralisib increased by over 173% when umbralisib was administered with food.

Using these mean values, a 334 mg oral dose of umbralisib under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of umbralisib under fed conditions in terms of exposure based on AUC_{0-inf}.

1.2.2.2.2 TGR-1202-PK102: FORMULATION EFFECT

Study TGR-1202-PK 102 was a two-period, randomized, two-way cross over, relative bioavailability and pharmacokinetic bioequivalence study with two different drug product formulations of umbralisib. In this study, umbralisib was administered under fasted conditions in 24 healthy subjects (12 males and 12 females) to assess the mean plasma umbralisib concentration over time following a 200 mg single dose of the original drug product formulation and modified (micronized) drug product formulation of umbralisib. The mean rate and extent of exposure to umbralisib were higher following administration of the micronized drug product formulation compared to the original drug product formulation as mean concentrations were higher throughout most of the samplinginterval.

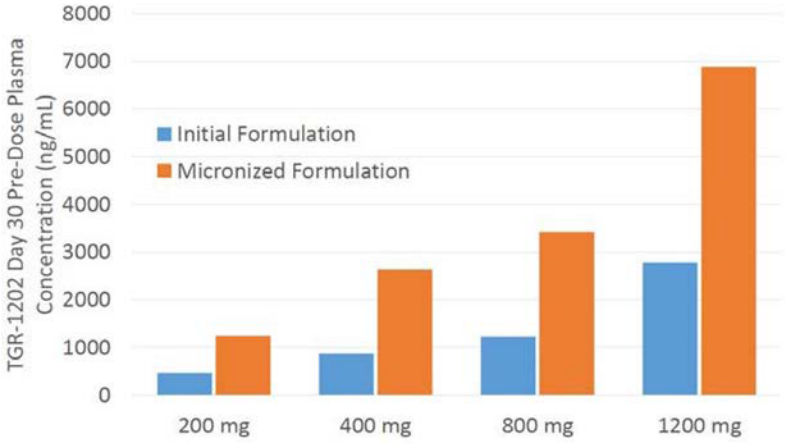
Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Original Formulatio	Micronized Formulatio		
AUC_{0-t} (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95
AUC_{0-inf} (ng·hr/mL)	7715.67	12378.19	160.43	146.49 – 175.70
C_{max} (ng/mL)	166.20	371.70	223.65	202.33 – 247.20

The micronized drug product formulation increased both the extent and rate of exposure of umbralisib under fasted conditions. The extent (AUC_{0-t}) and total extent (AUC_{0-inf}) of exposure both increased by 60%, respectively, following administration of the modified drug product formulation relative to original drug product formulation. The Peak plasma (C_{max}) levels of umbralisib increased by over 124% following administration of the micronized drug product formulation relative to original drug product formulation under fasted conditions.

Using these mean values, a 320 mg oral dose of umbralisib in the original formulation under

fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of the original formulation umbralisib under fasted conditions in term of exposure based on $AUC_{0\text{-}inf}$.

The improved exposure seen with the micronized formulation of umbralisib was confirmed in subjects in the Phase 1 dose escalation as well. The chart below illustrates the pre-dose plasma concentrations of umbralisib on Day 1 of Cycle 2 in subjects administered equivalent doses of either the initial formulation in the fasting state or the micronized formulation in the fed state:



1.3 UBLITUXIMAB

Ublituximab is a novel third generation chimeric anti-CD20 monoclonal antibody bioengineered for potent activity, exhibiting a unique glycosylation profile with a low fucose content, designed to induce superior antibody-dependent cytotoxicity (ADCC). Ublituximab exhibits competitive complement-dependent cytotoxicity (CDC), on par with rituximab, and has also been demonstrated to induce programmed cell death (PCD) upon binding to the CD20 antigen on B-lymphocytes. Ublituximab has a unique protein sequence, and targets epitopes on CD20 not targeted by rituximab or ofatumumab, both currently approved anti-CD20 antibodies (Esteves IT, 2011).

1.3.1 PRE-CLINICAL DEVELOPMENT OF UBLITUXIMAB

1.3.1.1 IN-VIVO ACTIVITY

In an in-vitro assay using B-CLL cells from subject donors, ublituximab demonstrated an enhanced ability to kill CLL cells compared to rituximab. Ublituximab demonstrated improved Fcγ receptor IIIA (FcγRIIIA)/CD16 binding and FcγRIIIA dependent effector functions compared to rituximab. Additionally, ublituximab induced higher in vitro ADCC against CLL cells, and a higher FcγRIIIA mediated interleukin-2 (IL2) production by FcγRIIIA+ Jurkat cells (de Romeuf C, 2008). Ublituximab demonstrated high ADCC against both subject-derived CLL cells and NHL cell lines. Ublituximab's engagement to FcγRIIIA triggers a stronger NK cell cytotoxicity against CLL as compared to rituxan (in vitro) despite CD20 density, likely related to the glycosylation pattern (de Romeuf C, 2008).

1.3.1.2 IN VIVO ACTIVITY

The antitumor effect of ublituximab was compared to that of rituximab with chemotherapy in follicular lymphoma (FL), and mantle cell lymphoma (MCL) xenograft murine models. Single agent ublituximab demonstrated dose-related anti-tumor activity with 100% tumor growth inhibition in

the FL xenograft at a dose of 100mg/kg, and a superior tumor growth delay (21 days) compared to rituximab. Ublituximab also demonstrated superior anti-tumor activity compared to rituximab against MCL xenografts at all dose levels (Esteves IT, 2011).

1.3.1.3 TOXICOLOGY

In single-dose and repeat dose toxicology studies performed under GLP, ublituximab displayed a safety profile similar to what might be expected for anti-CD20 monoclonal antibodies. Single administration of up to 100 mg/kg ublituximab in cynomolgus monkeys was well tolerated, with no local irritation with intravenous administration. Genotoxicity studies (Ames test) showed that ublituximab was not mutagenic. Monkeys that received a single injection of 0.3 mg/kg of ublituximab developed an anti-ublituximab response, whereas anti-ublituximab antibodies were not detected in the animals which received 10 or 100 mg/kg (see Ublituximab Investigator Brochure).

1.3.2 CLINICAL DEVELOPMENT OF UBLITUXIMAB

Ublituximab has been studied in a variety of subject populations, both as a single agent, and in combination with other agents, with over 100 subjects having received ublituximab therapy to date across all studies. Two Single-Agent Phase I/Ib trials have been conducted with ublituximab treating both NHL and CLL subjects, with a total of 41 subjects with relapsed or refractory CLL having been treated with single-agent ublituximab (TG-1101). Further, following demonstration of safety and tolerability in these early single agent studies, Phase I and II combination studies were undertaken with a variety of agents. Given the number of subjects who have received ublituximab in early-phase trials, the safety and side effect profile of the agent is well characterized. Summaries of the single-agent experience are provided below as well as data with use of ublituximab in combination with ibrutinib.

In a two part, first-in human dose escalation study (protocol CD20-0703), subjects with relapsed or refractory CLL received one weekly infusion of single agent ublituximab for 4 doses in a 3+3 dose escalation design through 5 sequential dose levels. Part II of the study was a dose-confirmation component which used an initial dose of 150 mg followed by 7 doses of 450 mg (total dose 3300 mg) – the clinical summary will focus on the Part II part of the study as the dose is more relevant to the clinical application used in current clinical studies. In Part II, 12 subjects were enrolled at 9 centers in France and followed for 12 months. Demographic data for the 12 subjects enrolled in the study were as follows. The median age was 69.5 years [62–77]; median time from diagnosis to inclusion was 10.4 years [4.0–23.6] and median prior therapies was 3 [1–8]. Seven subjects (58%) received at least one prior rituximab-containing regimen. The median lymphocyte bone marrow infiltration was 85% [40–94].

Most frequent drug-related adverse events (AE's) reported were infusion related reactions (IRR) (75% of the subjects, including 33% of subjects with Grade 3 IRR). Other Grade 3/4 AE's > 10% included: neutropenia (67%) and increase ALT/AST (17%). All AEs were reversible spontaneously or with supportive care intervention. None of the reported adverse events were considered as a dose-limiting toxicity according the judgment of the study Safety Committee. Therefore, the maximum tolerated dose was not reached in this study. Significant blood lymphocyte depletion was observed in all subjects: median lymphocyte count at baseline was 46.6 ($x10^9$/l); after 1 month (M1) = 1.5 (↓94%); M4=1.4 (↓91%) and M6=2.0 (↓89%). No cases of serum anti-ublituximab antibodies were detected at any time point.

Clinical response was based on the criteria established by the National Cancer Institute (NCI)-Working Group updated in 2008 (Hallek M, 2008). All subjects but one received the planned 8 infusions without any dose reduction--one subject was prematurely withdrawn due to a concomitant secondary leukemia unrelated to ublituximab therapy. Response was evaluated at month 4 for the 11 evaluable subjects, with an initial response rate of 64% (7/11) with a confirmed response at month 6 in 5/11 subjects (45%) subjects (all PRs). Four of the 11 subjects achieved stable disease. At the 1 year follow-up, no responders had progressed, demonstrating all confirmed responses were durable despite no ublituximab maintenance therapy. The median progression-free survival (PFS) was not reached at the 12 month follow-up (Cazin B, 2013).

A Phase I trial of ublituximab (NCT01647971) was subsequently undertaken in subjects with B-cell lymphoma who were relapsed or refractory to a prior rituximab containing regimen, which included 8 subjects with CLL. This trial utilized a 3+3 design, assessing dose levels of 450, 600, 900, and 1200 mg. No DLTs were observed amongst the 12 subjects enrolled into the dose-escalation component, and expansion cohorts were subsequently undertaken at 600, 900, and 1200 mg. Subjects with CLL were eligible to enroll into the expansion cohorts at 600 and 900 mg, receiving ublituximab on days 1, 8 & 15 of Cycles 1 & 2, with monthly mainte/nance infusions starting in Cycle 3, followed by every 3 months starting in Cycle 6.

Of the 8 CLL subjects enrolled, 4 had infusion related reactions that were manageable with infusion interruptions only and all subjects received all schedule doses. Other observed adverse events which were considered at least possibly related to study drug included neutropenia Grade 1/2 (n=1) and Grade 3/4 (n=3), as well as thrombocytopenia Grade 1/2 (n=1) and Grade 3/4 (n=1). Six subjects were evaluable for efficacy as of data cutoff for ASCO 2014, with 4 out of 6 subjects achieving a partial response. Rapid and profound circulating lymphocyte depletion (> 50% reduction) was noted with median time to peripheral response of 1 day (O'Connor OA, 2014).

1.3.2.1 PHARMACOKINETICS

After infusion of ublituximab (previously known as LFB-R603) at a 150 mg dose followed by seven weekly injection infusions at 450 mg, results suggested non-linear pharmacokinetics with respect to dose (450 mg vs. 150 mg) and time (week 4 vs. week 8) and more than proportional increase of Cmax and AUC∞ due to a clearance decrease. The volume of distribution at steady state was small (~5 L), approximately equal to blood volume. These non-linear pharmacokinetics may be explained by binding of ublituximab to its target, with a large component of target-mediated elimination after the first dose that is decreased after subsequent infusions due to a reduction in the available target. However, limited data for each dose level cohort and considerable variability in baseline subject characteristics, particularly in terms of tumor burden, make firm conclusions difficult.

The linear mean serum concentration-times profile after the first, the fourth and the eighth infusion of ublituximab are presented in Figure 4. A summary of non-compartmental PK parameters after the first, the fourth and the eighth infusion of ublituximab are presented in Table 1.

FIGURE 4: LINEAR MEAN SERUM CONCENTRATION-TIMES PROFILE AFTER THE FIRST, THE FOURTH AND THE EIGHT INFUSION OF UBLITUXIMAB

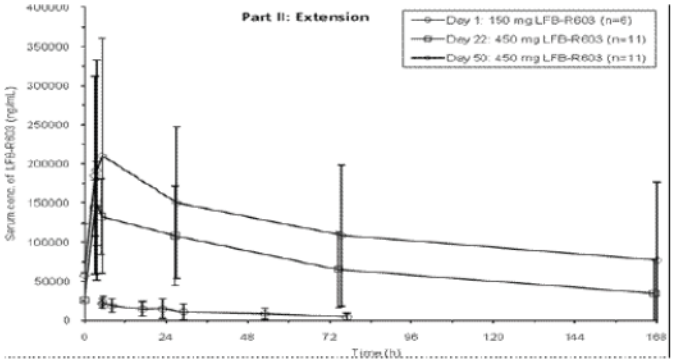


TABLE 1: PHARMACOKINETIC RESULTS AFTER THE 1ST (150 MG), THE 4TH (450 MG) AND THE 8TH (450 MG) INFUSION OF UBLITUXIMAB

PK Parameters [a]	1st Infusion 150 mg (Day 1)	4th Infusion 450mg (Day 22)	8th Infusion 450 mg (Day 50)
N	12	11	11
C_{max} (mg/L)	23.4 ± 11.2	168.6 ± 61.8	220.5 ± 141.9
t_{max} (h)	9.0 (5.0-30.3)	5.00 (3.1-52.0)	5.1 (3.1-23.5)
AUC_{∞} (mg.h/L)	732.1 ± 590	17890 ± 17730*	50760 ± 74460
$t_{1/2term}$ (h)	13.43± 10.2	80.7 ± 58.5*	147.8 ± 133.8
CL (mL/h)	424.2 ± 389.3	57.69 ± 42.91	38.62 ± 26.63
V_d/V_{dss}, (L)	4.8 ± 2.1	4.9 ± 2.3*	5.7 ± 3.3

[a] mean ± SD, t_{max}: median (range) , with respect to the start of infusion *Accurate determination not possible

Concentration was still measurable in at least one subject of the cohort up to day 169. Values for C_{max} and AUC_{∞} increased from the first to the eighth infusion whereas $t_{1/2}$ term decreased.

1.3.3 RATIONALE FOR THE PHASE 2 TRIAL

Treatment for newly diagnosed FL and SLL routinely includes chemotherapy based combinations, usually with a monoclonal antibody (Rituxan + Bendamustine or other chemo based regimens). Although effective, these chemotherapy- based regimens will often lead to relapse and unfavorable toxicities, especially for elderly subjects. New, novel treatments are needed which can be used in combination with monoclonal antibodies, that are chemotherapy-sparing with convenience of oral daily dosing.

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 been safely administered in subjects with various hematologic malignancies at doses up to and including 1200 mg QD.

Ublituximab (TG-1101) is a glycoengineered monoclonal antibody that binds to the trans-membrane antigen CD20 found on B-lymphocytes. The binding of ublituximab induces an immune response that causes lysis of B cells.

Ongoing studies are evaluating the ublituximab + umbralisib in subjects who previously relapsed from or are refractory to anti-CD20 antibody therapy as well as PI3K delta inhibitor therapy (Lunning, et. al. ASCO 2015, Fowler, et. al. ASCO 2015). A Phase 3, randomized study (UTX-TGR-304)

to assess efficacy and safety of ublituximab + umbralisib compared to obinutuzumab + chlorambucil in subjects with treatment naïve and relapsed/refractory CLL is currently ongoing with no observed safety trends reported (DSMB September 2018) in over 600 patients. To date, ublituximab and umbralisib either as single agents or in combination have been administered to over 1000 subjects worldwide.

As most trials to date have evaluated previously treated subjects, this trial will now evaluate umbralisib + ublituximab in treatment naïve FL and SLL subjects.

2 OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

PRIMARY OBJECTIVE

- To assess the overall response rate (ORR) in subjects with treatment naïve follicular lymphoma (FL) and small lymphocytic lymphoma (SLL) treated with umbralisib in combination with ublituximab.

KEY SECONDARY OBJECTIVES

- To evaluate the safety of umbralisib in combination with ublituximab.

- To assess the duration of response (DOR), Complete Response (CR) and progression-free survival (PFS) in subjects with treatment naïve follicular lymphoma and small lymphocytic lymphoma treated with umbralisib + ublituximab.

[redacted]

2.2 EFFICACY ENDPOINTS

Progression-free survival (PFS)

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. Definitive disease progression according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007).

Overall response rate (ORR)

ORR is defined as sum of CR and PR rates

Complete Response (CR) Rate

CR rate is defined as the proportion of subjects who achieve a CR.

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

Subjects 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

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

1. Treatment naïve, histologically-confirmed diagnosis of Follicular Lymphoma (FL) Grade 1, 2, or 3a, or Small Lymphocytic Lymphoma (SLL).
2. Subjects must have measurable or evaluable disease, and must have documented evidence for requiring treatment (bulky disease (>5 cm), high LDH, B symptoms, threatened organ function, splenomegaly, cytopenias due to lymphoma, or effusions).
3. Adequate organ system function, defined as follows:
   a. Absolute neutrophil count (ANC) ≥ 0.75 x 10^9/L. **Note:** No growth factors or transfusions are allowed to meet eligibility criteria.
   b. Platelets ≥ 50 x 10^9/L. **Note:** No growth factors or transfusions are allowed to meet eligibility criteria.
   c. Total bilirubin ≤1.5 times the upper limit of normal (ULN) with the exception of Gilbert's Disease and Autoimmune Hemolytic Anemia.
   d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement
   e. Creatinine ≤ 2.0 mg/dL OR calculated creatinine clearance (as calculated by the modified Cockcroft-Gault formula using ideal body mass [IBM] instead of mass) ≥ 30 mL/min
4. ECOG performance status ≤ 1.
5. Patients must be ≥18 years of age.
6. Ability to swallow and retain oral medication
7. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of either study drug.
8. Willingness and ability to comply with trial and follow-up procedures.

3.2 EXCLUSION CRITERIA

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

1. Subjects currently receiving systemic cancer therapy or previously received systemic cancer therapy for their lymphoma (i.e., chemotherapy, immunotherapy, biologic therapy, hormonal therapy, surgery, transplant, and/or tumor embolization).
2. Evidence of chronic active Hepatitis B defined as Hepatitis B surface antigen positive or Hepatitis B DNA positive by PCR (HBV, NOT including subjects with prior hepatitis B vaccination who are Hepatitis B surface antibody positive only;) or chronic active Hepatitis C infection (HCV) defined as Hepatitis C RNA positive by PCR, cytomegalovirus (CMV) DNA positive by PCR, or known history of HIV. If HBc antibody, HCV antibody or CMV IgG and/or IgM antibody is positive, subjects must be evaluated for the presence of HBV, HCV, or CMV by PCR - See Appendix F.
3. Subject has received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to Cycle 1/Day 1 or has not recovered from side effects of such therapy.
4. Primary central nervous system lymphoma (PCNSL) or known intracranial involvement, or leptomeningeal metastases.
5. Ongoing immunosuppressive therapy including systemic corticosteroids. Subjects are allowed to use topical or inhaled corticosteroids.
    a. Corticosteroid therapy started at least 7 days prior to Cycle 1/Day 1 (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted.
6. Known history of drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, or cirrhosis of the liver.
7. 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 (New York Heart Association functional classification III-IV)[see Appendix C- NYHA Classifications]
    b. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or 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. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting within 6 months of enrollment.
8. Malignancy other than Follicluar Lymphoma or SLL within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of Cycle 1/Day 1.
9. Women who are pregnant or lactating.

4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This is a Phase 2, open-label study of umbralisib, a PI3K delta inhibitor, administered in combination with ublituximab, a glycoengineered anti-CD20 mAb, to subjects with treatment naïve Follicular Lymphoma (FL) or Small Lymphocytic Lymphoma (SLL).

Daily doses of oral umbralisib will be administered for a duration of 24 cycles (approximately 24 months), in the absence of disease progression, unacceptable toxicity, or withdrawal from treatment. Two safety run-in cohorts of 3 - 6 subjects each at a dose of 600 mg and 800 mg umbralisib will first be enrolled to evaluate for key immune mediated toxicities. In the absense of unacceptable toxicity, enrollment will proceed with all subjects receiving 800 mg umbralisib. A fixed dose of 900 mg of ublituximab will be administered on Days 1, 8, and 15 in Cycle 1 and Day 1 of Cycles 2-6, Cycle 9 and 12. Ublituximab will be administered through Cycle 12. Treatment cycles are 28 days.

PET scans must be done at screening, within 14 days prior toCycle 6 Day 1, and to confirm CR (if applicable). During the study period, all subjects will be evaluated for response by CT (if contrast CT is contraindicated MRI with a non-contrast CT Chest should be completed) within 14 days of Day 1 of Cycles 3, 6, and 12. After Cycle 12, subjects should be evaluated for response by CT (if contrast CT is contraindicated MRI with a non-contrast CT should be completed), approximately every 6 cycles through cycle 24, unless clinically indicated sooner (at the discretion of the treating physician).

After 24 cycles (approximately 24 months) of treatment, subjects will discontinue study medication and be followed for progression-free survival. Subjects who discontinue study drugs will have an End of Treatment visit within 30 days from the last dose of study drug. After cycle 24, subjects should have response assessment at least every 12 months or more frequently as medically indicated.

Subjects who discontinue from study treatment (for reasons other than progressive disease or completion of therapy), will have an End of Treatment visit within 30 days from the last dose of study drug. Follow for PFS as below:

- Months 1-24 approximately every 6 months
- Months 25 and beyond at least every year

Safety will be evaluated continuously throughout the study.

Up to 50 subjects are expected to be enrolled in this study.

4.2 SAFETY RUN-IN

A 3 + 3 approach will be utilized to evaluate safety during the safety run-in phase. Three subjects will first be treated at 600 mg umbralisib in combination with ublituximab for 1 cycle (28 days). If 1/3 subjects experience an unacceptable toxicity (defined below), 3 additional subjects will be enrolled at the same dose level. If >1/6 subjects at 600 mg experience an unaceptable toxicity, it

will be deemed to exceed the MTD and enrollment to the study will stop. If ≤1/6 subjects experience an unacceptable toxicity at 600 mg, then 3 subjects will be enrolled to receive 800 mg umbralisib in combination with ublituximab for 1 cycle (28 days). If 1/3 subjects experience an unacceptable toxicity, 3 additional subjects will be enrolled at the same dose level. If >1/6 subjects at 800 mg experience an unaceptable toxicity, it will be deemed to exceed the MTD and enrollment to the remaineder of the study will proceed at 600 mg umbralisib. If ≤1/6 subjects experience an unacceptable toxicity at 800 mg, then enrollment will proceed for the remainder of the study at 800 mg umbralisib.

An unacceptable toxicity will be defined as the occurance of transaminitis, colitis, pneumonitis, or rash during Cycle 1 that is:

- Grade ≥3 and persists for >7 days without resolution despite supportive care; or
- Any grade treatment emergent toxicity that results in treatment discontinuation.

4.3 REGISTRATION AND ENROLLMENT

Prior to participation, subjects must willingly consent to the study after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Only eligible subjects will be enrolled onto the study.

Investigators will use an interactive web response system (IWRS) to register and enroll subjects to study UTX-TGR-203. Upon entering subject information into the IWRS, investigators will receive a unique subject identifier. This confirmation must be received by the site prior to dispensing study drug to the participant. Further details about the subject registration process using the IWRS system will be outlined in the Study Manual.

4.4 STUDY SITES

Up to 15 trial centers in the United States may participate in this study. Enrollment is expected to be completed in approximately 12-16 months.

4.5 DISCONTINUATION FROM STUDY TREATMENT

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

- Disease progression
- Intolerable toxicity related to study drug
- Subject requests to withdraw consent or discontinue treatment
- Pregnancy
- Inability of the subject 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 by the Sponsor
- Completion of 24 months of therapy

Subjects who discontinue from study treatment (for reasons other than progressive disease or

completion of treatment) should continue to be followed for progression-free survival (PFS).

Follow for PFS as below:

- Months 1-24 approximately every 6 months
- Months 25 and beyond at least every year

After withdrawal from protocol treatment, subjects should be followed for AEs for 30 calendar days after their last dose of either 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 subject's medical records and as a comment on the electronic Case Report Form (eCRF).

All subjects 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 subject's medical records and as a comment on the eCRF.

5 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

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

Cycle = 28 days	Screen	Cycle 1			Cycles 2-6					> Cycle 6	End of study[1]	LTFU
					C2	C3	C4	C5	C6	C9, 12, 18 and 24		
Procedure\Days	**-28-1**	**D1[2]**	**D8**	**D15**	**Day 1**					**Day 1**		
Medical history	X											
ECOG Performance Status[3]	X	X			X	X	X	X	X	X	X	
Physical examination[3]	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (pulse, BP, temp, weight, resp)	X	X	X	X	X	X	X	X	X	X	X	
BM Biopsy/aspirate[4]	X											
12-lead EKG	X											
Tumor evaluation[5]	X[5]					X[5]			X[5]	X[5]		X[5]
FLIPI Staging[6]	X											
Serology: HCV, HBV, CMV[7]	X											
CMV Surveillance[8]						X			X	X		
Hematology (CBC including 5-part differential and platelets)[9]	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[10]	X	X	X	X	X	X	X	X	X	X	X	
Cholesterol, LDL, HDL & Triglycerides[11]	X	X			X	X	X	X	X	X	X	
PT/INR	X											
Serum Pregnancy Test[12]	X											
Urine Pregnancy Test	X				X		X		X	X		
Core needle biopsy (optional)[13]	X			X								
Lymphocyte subsets[15]		X			X	X	X	X	X	X	X	
PK Sampling (all pre-dose)[16]		X		X	X	X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
AE Evaluation	X	X	X	X	X	X	X	X	X	X	X	
Ublituximab		X	X	X	X	X	X	X	X	X[17]		
Umbralisib (TGR-1202)		Administered orally daily with food through Cycle 24[18]										

[redacted]

[1] All subjects should undergo the end-of-study assessments listed within 30 days after treatment ends.

[2] Cycle 1/Day 1 procedures are all pre-dose study drug.

[3] The screening physical examination, ECOG PS, cholesterol, LDL, HDL & triglycerides must be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. Include assessment of B-symptoms. C1 (Day 8 & 15) and Cycle 2 (Day 1) physical exams have a ± 3 day window, and a ± 7 days for all visits after Cycle 2.

[4] Subjects should have a bone marrow biopsy and/or aspirate within 90 days prior to Day 1 of Cycle 1 according to standard of care guidelines. Bone marrow biopsy and/or aspirate should also be obtained to confirm a CR. Bone marrow biopsy and aspirates should include FISH, flow cytometry and cytogenetics.

[5] Baseline scans should be completed within 30 days prior to Day 1 of Cycle 1. All tumor evaluations after baseline have a +/- 14 day window. Radiology assessment includes a contrast enhanced CT scan of chest, abdomen, and pelvis (and neck as clinically warranted). If iodinated contrast is contraindicated, a non-contrast chest CT coupled with a gadolinium-enhanced MRI of the abdomen/pelvis (and neck as clinically warranted) is an acceptable substitute. PET using fluorodeoxyglucose (FDG) should be done at screening for all subjects then within 14 days of Cycle 6 and to confirm potential CR. Tumor evaluation should occur within 14 days of Day 1 of Cycles 3, 6, and 12, and approximately every 6 cycles thereafter through cycle 24. During LTFU, assessments should occur approximately every 12 months.

[6] Lymphoma staging should be captured (see Appendix E) at baseline.

[7] Serum virology to include HBsAg, HBc antibody, HCV antibody and CMV IgG and IgM. If HBc antibody, HCV antibody or CMV IgM is positive, subjects must be evaluated for the presence of active HBV, HCV or CMV by DNA(PCR) Serum virology to include HBsAg, HBc antibody, HCV antibody and CMV.

[8] CMV only should be checked by PCR approximately every 3 cycles, as part of the subject's scheduled visit. If subject is CMV positive, stop therapy and provide supportive care per investigator discretion. CMV surveillance should discontinue 30 days after last dose of umbralisib.

[9] The screening hematology must be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. C1 (Day 8 & 15) and Cycle 2 (day 1), laboratory assessments have a ± 3 day window, and a ± 7 days for all visits after Cycle 2. Hematological parameters include the following laboratory tests: complete blood count consisting of hmeatocrit, hemoglobin, total white blood count (WBC) with 5-part differential, and platelet count.

[10] The screening chemistry must be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. C1 (Day 8 & 15) and Cycle 2 (Day 1) laboratory assessments have a ± 3 day window, and ± 7 days for all visits after Cycle 2. Chemistry panel includes the following: urea or blood urea nitrogen, creatinine, sodium, potassium, calcium, carbon dioxide, magnesium, phosphorous, glucose, albumin, total protein, total bilirubin, alkaline phosphatase, AST, ALT, GGT, uric acid, and lactate dehydrogenase.

[11] To be done ≤ 7 days prior to initial of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated.

[12] For women of child-bearing potential, a serum prenancy teset will be performed at baseline (within 72 hours of Day 1 of Cycle 1) with a urine pregnancy test D1 of each cycle.

[13] Core needle biopsy optional. If collected, sample at pre-dose (within 28 days) and one post dose anytime between Days 15 & 28 of Cycle 1.

[redacted]

[15] Peripheral blood for lymphocyte subsets will be drawn on Cycle 1 Day 1 (pre-dose), Day 1 of Cycles 2-6, 9, 12, 18 and 24 and at end of study.

[16] PK samples (plasma) will be collected according to the schedule in Section 5.1.2 (Central Laboratory Assessments). Additional PK samples may be collected outside of this schedule upon the occurrence of toxicity in order to correlate to plasma concentrations.

[17] Ublituximab infusion only in Cycle 9 & 12 – no additional ublituximab after Cycle 12.

[18] Review study drug compliance and document missed doses in medical record. Subjects are required to start prophylaxis treatment for pneumocystis jiroveci pneumonia (PCP) as well as antiviral therapy prior to Cycle 1 Day 1.

5.1 LABORATORY ASSESSMENTS

Laboratory assessments will be collected as specified in the study assessments and treatment schema and both Central and Local Laboratories will be utilized. Please refer to the lab manual for detailed instructions outlining procedures (ie- collection, preparation, shipping) for both local and central laboratories.

5.1.1 LOCAL LABORATORY ASSESSMENTS

1. Hematologic profile and serum chemistry to include:

Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	Absolute lymphocyte count
Erythrocyte count	Monocytes	Leukocyte count
Basophils	Eosinophils	Absolute neutrophil count
Serum Chemistry		
Albumin	Glucose	SGOT [AST]
Alkaline phosphatase	GGT	SGPT [ALT]
Bicarbonate/CO2	LDH	Total bilirubin
BUN	Magnesium	Total protein
Creatinine	Phosphorus	Uric Acid
Chloride	Potassium	
Calcium	Sodium	

2. Serum and urine pregnancy test.
3. Coagulation lab tests to include PT and INR.
4. Cholesterol, LDL, HDL and Triglycerides will be done at timepoint specified in the Study Assessment table
5. Serum Virology to include HBsAG, HBc antibody, HCV antibody, and CMV IgG and IgM. If HBc antibody, HCV antibody or CMV are positive the subject must be evaluated for the presence of active HBV, HCV or active CMV IgM by DNA (PCR). CMV should be checked by PCR approximately every 3 cycles as part of the subject's scheduled visit. If subject is CMV positive, stop therapy and discuss intervention with medical monitor CMV suveillance will discontinue 30 days after last dose of umbralisib (EOT visit)..- See Appendix F.
6. Subjects with low-grade lymphoma should have a baseline bone marrow aspirate and/or biopsy prior to study entry, according to standard of care guidelines, and then to confirm CR. Bone marrow biopsy and aspirates should include FISH, flow cytometry and cytogenetics.

5.1.2 CENTRAL LABORATORY ASSESSMENTS

The following assessments will be shipped to and analyzed at a central laboratory. Please see Lab Manual for processing, handling, and shipping instructions.

5.1.2.1 LYMPHOCYTE SUBSETS

Peripheral blood for lymphocyte subsets will be drawn at the scheduled time points listed below.

LYMPHOCYTE SUBSET COLLECTION TIMES

Scheduled time point
Cycle 1 Day 1 (pre-dose)
Cycle 2 Day 1
Cycle 3 Day 1
Cycle 4 Day 1
Cycle 5 Day 1
Cycle 6 Day 1
Cycle 9 Day 1
Cycle 12 Day 1
Cycle 18 Day 1
Cycle 24 Day 1
End of Study

5.1.2.2 PHARMACOKINETIC BLOOD SAMPLES

PK blood (plasma) samples will be taken at the following timepoints during the dose-finding portion of the study. Additional PK samples may be collected outside of this schedule upon the occurrence of toxicity in order to correlate to plasma concentrations.

PHARMACOKINETIC COLLECTION TIMES

Visit	Scheduled time point
Cycle 1 Day 1	Pre-dose
Cycle 2 Day 1	Pre-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

[redacted]

6 TREATMENT PLAN

6.1 TREATMENT SUMMARY

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

UMBRALISIB (TGR-1202)

- 600 mg (safety run-in cohort) or 800 mg once daily through Cycle 24 (approximately 24 months). No additional umbralisib will be administered after Cycle 24.
- Subject diary will be utilized. Missed doses of umbralisib should be noted by the subject on the subject diary. In addition, drug accountability should be documented in the subjects medical record.

UBLITUXIMAB

- 900 mg Ublituximab on Days 1, 8, 15 of Cycle 1 and Day 1 of Cycles 2-6, Cycle 9 and 12. No additional ublituximab will be administered after Cycle 12.

6.2 AGENT ADMINISTRATION

6.2.1 GUIDELINES FOR ADMINISTRATION OF UMBRALISIB

- *Method of Administration:* Umbralisib will be administered orally once daily with food.
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:* Subjects are required to start prophylaxis treatment for pneumocystis jiroveci pneumonia (PJP) as well as antiviral therapy prior to Cycle 1 Day 1.
    - *Anti-viral Prophylaxis*: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent
    - *PJP Prophylaxis:* Dapsone 100 mg daily
- Final choice of PCP and anti-viral prophylaxis therapy is per investigator discretion.

NOTE: If PJP or anti-viral therapy is not tolerated, alternate to a different PJP or anti-viral therapy, discontinue, or reduce dose/schedule as per the discretion of the investigator.

Umbralisib will be dispensed at the sites by the research coordinator or designee under the direction of the PI or by a pharmacist at the site. Subjects must be provided drug in its original container. Subjects should be instructed to return any unused tablets when they return the bottle to the site. A drug diary should be provided to the subject. Study drug compliance should be reviewed with the subject at the beginning of each new treatment cycle and as needed. Missed doses will be documented in the subjects' medical record.

Umbralisib will be self-administered (by the subject). Tablets should be taken at approximately the same time each day with food (within 30 minutes of a meal). Subjects 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 a period of 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 pharmacist or his/her representative should record all umbralisib drug dispensations in the electronic drug accountability log. When doing this, the complete record should be logged. This includes the subject number, subject initials, date of dispensation, and lot number of the individual bottle.

The exact dose and the date of administration of umbralisib must be recorded within the eCRF and the subject's medical records. For the purpose of drug accountability and dosing, a drug diary will be utilized. Any error in drug administration should be recorded (e.g., missed dose) in the eCRF.

6.2.2 GUIDELINES FOR ADMINISTRATION OF UBLITUXIMAB

- *Method of Administration:* Ublituximab will be administered as an intravenous infusion through a dedicated line.
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:* Ublituximab should be started approximately 30 minutes after the conclusion of the last pre-medication infusion and should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). If pre-medication is given orally, they should be given approximately 45-60 minutes prior to the beginning of the ublituximab infusion. If subject has a negative reaction to a premedication, change to an equivalent drug, decrease dose, or discontinue if subject cannot tolerate. Additionally, if subject has other health conditions that are adversely impacted by the premedication drug (s) consider changing drug/dose, or discontinuing if investigator feels it is in the subjects best interest.
    - Use of oral acetaminophen 650 mg (or equivalent) should be restricted to subjects who experience fever or pyrexia after week 1 dose, or as clinically warranted.
    - If after cycle 6, use of a corticosteroid is of clinical concern, please contact sponsor.
- *Hypersensitivity and Infusion Reaction Precautions*: Medication and resuscitation equipment must be available per institutional guidelines prior to ublituximab administration for the emergency management of potential anaphylactic reactions.
- *Subject Care Implications*:
    - Ublituximab should not be administered as an IV push or bolus.
    - Ublituximab may be administered on an outpatient basis.
    - Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab should not be administered if does not conform to the

specifications. Immediately inform the Monitor/Sponsor with any product quality concerns or questions.

- It is recommended that ublituximab be administered immediately after dilution.
- No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).
- Concurrent glucocorticoid therapy as long as started for at least 7 days prior to study entry (≤ 10 mg per day of prednisone or equivalent) is allowed as clinically warranted.
- Since infusion-related hypotension may occur, **antihypertensive medications should be withheld 12-24 hours prior to and throughout infusion of ublituximab at investigator discretion.**
- For subjects at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

6.2.2.1 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE - UBLITUXIMAB

Infusion related reactions including severe reactions have been reported with ublituximab administration. Guidelines are provided below for subjects who experience such reactions. Symptomatic infusion reactions, despite premedication, may be treated at the discretion of the treating physician, including but not limited to: oral acetaminophen 650 mg (or equivalent), corticosteroids, antihistamines, oxygen, and bronchodilators.

The following are recommended infusion rate reduction/delay guidelines for subjects who experience severe Infusion Related Reactions (IRR's) in which treatment should be interrupted. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator.

1st or 2nd Infusion Interruption:

- Hold infusion and closely monitored subject, institute symptomatic medical management until resolution of IRR symptoms.
- Following the judgment of the Investigator, and provided the subject is stable, the infusion may be resumed at no more than half the previous rate.
- If the subject does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate at the treatment cycle dose (see Section 6.2.2.2.

3rd Infusion Interruption (same day):

- Discontinue infusion for that day – monitor subject for resolution of all symptoms. Subject should have all vital signs completed as well as any other standard of care procedures completed as warranted by the Investigator prior to release of subject from study site.
- Any remaining diluted investigational product should be discarded.

If an infusion related reaction is observed, at any time during the ublituximab treatment, the treating investigator may reduce the infusion flow rate at their discretion.

6.2.2.2 FLOW RATE RECOMMENDATIONS FOR UBLITUXIMAB ADMINISTRATION

Cycle 1 infusion over 4 hours

Cycle 1	Ublituximab Dose	Total volume to be infused	Infusion rate			
			T0 to T30'	T30' to T1H	T1H to T2H	T2H to T4H
Day 1	900 mg	500 mL	10 mL/H	20 mL/H	85 mL/H	200 mL/H

Cycle 1 Day 8 & 15 infusions over 3 hours

Ublituximab Dose	Total volume to be infused	Infusion rate		
		T0 to T1H	T1H to T2H	T2H to T3H
900 mg	500 mL	50 mL/H	150 mL/H	300 mL/H

Cycle 2 and remaining infusions over 90 minutes

Ublituximab Dose	Total volume to be infused	Infusion rate	
		T0 to T30min	T30min to T90min
900 mg	500 mL	200 mL/H	400 mL/H

6.2.2.3 DISPENSING OF UBLITUXIMAB

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

The exact dose of ublituximab as well as the date and time of administration must be recorded within the eCRF, the subject's medical records, and/or in the drug accountability records.

The pharmacist or his/her representative should record all ublituximab drug dispensations in the drug accountability log. When doing this, the complete record should be logged. This includes the subject number, subject initials, date of dispensation, and lot number of the individual vial.

Preparation should be done by the Pharmacist or his/her representative according to instructions for sterile dilution.

6.2.2.4 DILUTIONS OF UBLITUXIMAB

Ublituximab should not be mixed with other medicinal products. Ublituximab should only be diluted in 0.9% NaCl before use. [redacted].

[redacted]

Dilutions for ublituximab infusions for vials that contain 6 mL (25 mg/mL)

Dose of ublituximab for infusion	[redacted]
900 mg	

6.2.3 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that subject has:

- No intolerable toxicities related to study drug.
    - Treatment may be delayed to recover from toxicity
- No clinical or radiographic evidence of disease progression.
- Not withdrawn from the study for other reasons.

6.3 DOSING DELAYS AND MODIFICATIONS

Subjects should be assessed clinically for toxicity at each visit using the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE) grading scale. Dosing will occur only if a subject's clinical assessment and laboratory test values are acceptable.

At the discretion of the Investigator, a dose re-escalation may be permitted for subjects who were dose reduced upon resuming umbralisib. Subjects that require dose reduction for events that are life-threatening should not be re-escalated. On second dose reduction for the same event contact the Medical Monitor prior to dose re-escalating to discuss management of the subject.

Holidays from study drug are discouraged. However, for subjects requesting a drug holiday without an adverse event, a holiday may be permitted at the discretion of the Investigator. The subject must be on study drug for 3 months to be eligible for a holiday from study drug >4 weeks.

Any subject in whom similar toxicity recurs at the reduced dose should be discontinued from further umbralisib treatment. Exceptions to this discontinuation rule on the basis of ongoing clinical benefit and acceptable/minimal clinical risk may be allowed following a careful assessment and discussion of risk versus benefit with the subject by the Investigator and with approval from the Medical Monitor.

If a subject discontinues only one study drug, the subject may continue treatment with the other study drug per the protocol. Please see Sections 6.3.1 and 6.3.2 below for specific guidelines regarding dose delay and/or modifications. Contact the sponsor prior to discontinuing any study drug(s).

6.3.1 DOSE DELAY/MODIFICATIONS: UMBRALISIB

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. Delay for recovery from toxicity is allowed for both study drugs (ublituximab and/or umbralisib) for recovery of hematologic toxicities to ≤Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If the subject withdraws consent or has documented progression, an end of study visit should be completed.

If a subject discontinues only one study drug, the subject may continue treatment with the other study drug per the protocol.

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 recurrence or persistent Grade 3, resume at next lower dose level at discretion of the investigator.
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 recurrence after re-challenge, resume at next lower dose level at discretion of the investigator.
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 re-challenge, resume at next lower dose level at discretion of the investigator.
Pulmonary & Related Infections*	
Grade 2	Stop all therapy and hold until resolution. Restart umbralisib at current dose or one lower dose level per PI discretion. Subjects with Grade 1 or 2 pneumonitis must restart at one lower dose level. If recurrence after re-challenge, resume at next lower dose level at discretion of the investigator.
Grade ≥3	Stop all therapy and hold until resolution. Restart umbralisib at one lower dose level per PI discretion. Subjects with Grade ≥3 pneumonitis must discontinue therapy.
***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.** ***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 viral prophylaxis is required at start of therapy.**	
All Other Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level. NOTE: If persistent grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ grade 1. If recurrence after re-challenge, resume at full dose or next lower dose level at discretion of the investigator.
Grade ≥3	Withhold umbralisib until Grade ≤2. If recurrence after re-challenge, resume at full dose or next lower dose level at discretion of the investigator.
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 full dose or next lower dose level at discretion of the investigator.

Diarrhea Grade ≥3	Withhold umbralisib until Grade ≤2. Resume at full dose or next lower dose level as per discretion of investigator If recurrence after rechallenge, resume at next lower dose level at discretion of the investigator.
Colitis (all Grades)	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level
Liver Toxicity (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Grade 1	• Maintain current dose • Assess Concomitant Medications and Risk Factors* • Monitor Labs every 1-2 weeks
Grade 2	• Maintain current dose • Assess Concomitant Medications and Risk Factors* • Begin supportive care (prednisone 0.5-1 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 once off steroids, re-initiate steroids with 10 mg per week taper until off. ○ Consider withholding umbralisib.
Grade >3	• Hold umbralisib • Assess Concomitant Medications and Risk Factors* • Begin/continue supportive care (0.5-1 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 • Resume umbralisib at next lower dose level when Grade ≤1
* 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.	

STUDY DRUG DOSE REDUCTION RECOMMENDATIONS

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 subject 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 must 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.

6.3.2 DOSE DELAY/MODIFICATIONS: UBLITUXIMAB

No reduction in the dose of ublituximab is permitted. Please refer to Section 6.2.2.1 for detailed information on infusion rate guidance for infusion related reactions related to ublituximab.

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. A delay for recovery from toxicity is allowed for both study drugs (individually or together) for recovery of hematologic toxicities to ≤Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. subjectIf the subject withdraws consent or has documented progression, an end of study visit should be completed.

If Grade 4 anaphylaxis is observed at any point during ublituximab treatment, permanently discontinue ublituximab treatment and intervene as per investigator discretion.

If a subject discontinues only one study drug (either ublituximab or umbralisib), the subject may continue treatment with the other study drug per the protocol. **Contact the sponsor prior to discontinuing the study drug(s).**

TABLE 3: UBLITUXIMAB DOSE DELAY AND/OR MODIFICATIONS GUIDANCE

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 3 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay ublituximab until Grade ≤ 3 and/or neutropenic fever or infection is resolved; consider growth-factor support as warranted; thereafter, resume at full dose.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay ublituximab until Grade ≤ 3; consider intervention with supportive care as warranted; thereafter resume at full dose.
Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose.
Grade ≥3	Withhold ublituximab until Grade ≤ 2 at the discretion of the investigator; consider supportive care intervention as warranted. Resume at full dose.

6.4 ORDERING UBLITUXIMAB AND UMBRALISIB

Once a clinical study site receives the open to enrollment letter and a subject is identified, a pre-determined quantity of ublituximab and umbralisib will be shipped to the site.

Upon receipt of this shipment, the Pharmacist or the appropriate person at the site should update the accountability forms for both ublituximab and umbralisib. If there is any abnormality in the supplied boxes (ublituximab) or bottles (umbralisib), the Pharmacist or the appropriate person must document it during the acknowledgement of receipt and contact the Sponsor and/or Sponsor designee.

6.5 DURATION OF THERAPY

Subjects will visit the study center as per the treatment schedule that is included in the protocol. All visits should occur as close as possible to the time specified in the protocol. Complete listings of the assessments that will be performed at each visit, during the trial treatment period, are specified in Section 5.

In the absence of treatment delays due to adverse event(s), umbralisib and ublituximab should continue as per the treatment plan unless one of the following criteria applies:

- Disease progression or inter-current illness that prevents further treatment.
- Subject decides to withdraw from the study, or changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

7 STUDY MEDICATION OVERVIEW AND SAFETY

7.1 UMBRALISIB (TGR-1202)

Classification:	Phosphatidylinositol-3-Kinase (PI3K) Delta Inhibitor
Formulation:	See Investigator Brochure
Mode of Action:	Irreversibly inhibits activity of the Class I Delta isoform of PI3K
How Supplied:	Umbralisib: 200 mg tablets
Storage:	Store at 25°C. Excursions permitted 15°C to 30°C.
Stability:	Retest dates will be provided periodically by Sponsor.
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.

7.2 UBLITUXIMAB

Chemical Name:	Ublituximab
Other Names:	TG-1101
Classification:	Recombinant chimeric anti-CD20 monoclonal antibody
Mode of Action:	Targets CD20 antigen on B-cells
Description:	Ublituximab is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen found on the surface of B lymphocytes. Ublituximab displays the typical structure of immunoglobulins, consisting of two gamma (γ) heavy chains and two kappa (κ) light chains linked by disulfide bridges. It is composed of a murine variable region (37.2% of total amino acids) fused onto human constant regions.
How Supplied:	Concentration of 25mg/mL in 6 mL (150 mg) single-use glass vials.
Storage:	Ublituximab must be stored in a secured, limited-access, refrigerated area at a temperature ranging from +2°C / + 8°C. Ublituximab must not be frozen.

Stability: Once a vial of ublituximab has been opened and/or diluted it must be used immediately. After dilution, ublituximab is stable in static conditions for 24 hours at 25°C, and in dynamic conditions it is stable for 8 hours at 25°C.

Ublituximab has a shelf-life of 36 months if stored between +2°C / + 8°C, based on stability data.

Route of Administration: Intravenous

Packaging: Ublituximab is packed in kits. Each kit contains:

- Six vials containing 150 mg solution of ublituximab in each
  or
- One vial containing 150 mg solution of ublituximab (for replacement if needed)

The container closure system for the vials containing 6 mL is a type I glass vial closed by a siliconized chlorobutyl rubber stopper sealed with an aqua plastic and aluminum cap

Availability: Ublituximab is available from TG Therapeutics.

7.2.1 UBLITUXIMAB + UMBRALISIB (TGR-1202) COMBINATION - COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in subjects treated with the combination of ublituximab + umbralisib and were considered at least possibly related to one or both of the study medications. The preliminary safety data as of May 1, 2018 is provided for a total of 75 subjects exposed to ublituximab + umbralisib with a maximum follow up of 3+ years. See the latest ublituximab and umbralisib Investigator's Brochures for updated safety information a complete list of all adverse events reported regardless of causality. .

7.2.1.1 VERY COMMON (≥ 10%):

Blood and Lymphatic System Disorders: anemia, neutropenia

Gastrointestinal Disorders: diarrhea, nausea, vomiting

General Disorders and Administration Site Conditions: fatigue

Injury, Poisoning and Procedural Complications: infusion related reaction

Metabolism and Nutrition Disorders: decreased appetite

7.2.1.2 COMMON (≥ 1% - < 10%):

Blood and Lymphatic System Disorders: thrombocytopenia

Cardiac Disorders: cardiac failure congestive

Ear and Labyrinth Disorders: ear congestion, ear discomfort

Eye Disorders: conjunctival pallor, conjunctivitis, corneal oedema, vision blurred

Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastrooesophageal reflux disease, haematochezia, salivary hypersecretion, stomatitis

General Disorders and Administration Site Conditions: asthenia, chills, face oedema, infusion site pain, local swelling, odedema peripheral, pyrexia, systemic inflammatory response syndrome

Hepatobiliary Disorders: hyperbilirubinaemia

Immune System Disorders: hypogammaglobulinaemia

Infections and Infestations: bronchitis, cellulitis, clostridium difficile colitis, enterocolitis infectious, oral candidiasis, oral herpes, otitis media, pneumonia, pneumonia streptococcal, rhinovirus infection, sepsis, sepsis syndrome, sinusitis, skin infection, upper respiratory tract infection, urinary tract infection

Injury, Poisoning and Procedural Complications: wound

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, computerised tomogram thorax abnormal, immunoglobulins decreased, weight decreased

Metabolism and Nutrition Disorders: dehydration, failure to thrive, hyperglycaemia, hyperuricaemia, hypokalaemia, hypophosphataemia

Musculoskeletal and Connective Tissue Disorders: joint swelling, muscle spasms, muscular weakness, myalgia, pain in extremity

Nervous System Disorders: dizziness, dysgeusia, headache, lethargy, sinus headache, somnolence

Psychiatric Disorders: agitation, anxiety

Renal and Urinary Disorders: micturition urgency, renal failure, renal failure acute

Reproductive System and Breast Disorders: scrotal cyst, semen discolouration

Respiratory, Thoracic and Mediastinal Disorders: choking, cough, dysphonia, dyspnea, epistaxis, hypoxia, oropharyngeal pain, pneumonitis, productive cough, sinus congestion

Skin and Subcutaneous Tissue Disorders: alopecia, cold sweat, dermatitis acneiform, dermatitis bullous, dry skin, ecchymosis, pruritus, rash, maculo-papular, rosacea, urticaria

Vascular Disorders: hypertension

8 MEASUREMENT OF EFFECT

PET scans must be done at screening, within 14 days of Cycle 6 Day 1, and to confirm CR (if applicable). During the study period, all subjects will be evaluated for response by CT (if contrast CT is contraindicated MRI with a non-contrast CT Chest should be completed) within 14 days of Day 1 of Cycles 3, 6, and 12. After Cycle 12, subjects should be evaluated for response by CT (if contrast CT is contraindicated MRI with a non-contrast CT Chest should be completed) approximately every 6 cycles through cycle 24 unless clinically indicated sooner (at the discretion of the treating physician). Subjects achieving stable disease or better should continue daily treatment with umbralisib for a duration of 24 cycles (approximately 24 months). Response assessmets for PFS after cycle 24 should occur at least every 12 months. All baseline assessments to characterize disease will be performed within 30 days of Cycle 1 Day 1, prior to initiation of therapy. During the treatment period, all efficacy assessments have a +/- 14 day window. The determination of response and progression will be based on the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson et al., 2007, See Appendix D) modified so that the six index lesions include both nodal and extranodal lesions as described in the Lugano classification (Cheson et al. 2014) rather than considering nodal and extranodal lesions separately.

Subjects will remain on study treatment (for a duration of 24 months) until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue from study treatment for any reason other than PD will continue to be followed for progression, as per the protocol.

8.1 METHOD OF ASSESSMENT

CT scan is the preferred method for radiographic tumor assessment. CT with iodinated IV contrast is preferred. If iodinated contrast is contraindicated, a non-contrast chest CT coupled with a gadolinium-enhanced MRI of the abdomen/pelvis (and neck as clinically warranted) is an acceptable substitute. Chest x-ray, ultrasound, endoscopy, laparoscopy, or tumor markers will not be considered for response assessment. PET using fluorodeoxyglucose (FDG) should be done at screening for all subjects, approximately 14 days of Day 1 of Cycle 6 and then to confirm a potential CR for subjects with FDG-avid disease.

Bone marrow assessment should be used to assess response to therapy if the subject was deemed to have disease in the bone marrow prior to initiation of protocol therapy and at the discretion of the investigator.

For radiographic evaluations, the same method of assessment and the same technique (e.g., scan type, subject 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 subject is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless medically contraindicated.

All baseline assessments to characterize disease will be performed within 30 days of Cycle 1 Day 1, prior to initiation of therapy.

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 the Sponsor requests to confirm any objective response observed.

8.3 ANTITUMOR EFFECT

Assessment of lymphoma response (CR, PR or SD) and disease progression will be evaluated as outlined in the schedule of events, according to the Revised Response Criteria for Malignant Lymphoma for NHL subjects (Cheson et al., 2007). Overall response rate, CR, PR, SD, PFS and DOR will be calculated as detailed below.

8.4 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Evaluable for objective response. Only those subjects who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

8.4.1 COMPLETE RESPONSE

Complete response (CR) is defined as the complete disappearance of all evidence of disease and disease-related symptoms. The spleen and/or liver, if considered enlarged before therapy, on the basis of physical exam or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. Bone marrow infiltrate cleared on repeat biopsy, if indeterminate by morphology, immunohistochemistry should be negative (Cheson et al., 2007).

In subjects with FDG-avid lymphoma with a positive PET scan before therapy or no pretreatment PET scan, a post-treatment residual mass of any size is permitted as long as it is PET negative. In subjects with variably FDG-avid lymphomas or where FDG-avidity is unknown, all lymph node and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in the long axis and more than 1.0 cm on their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment (Cheson et al., 2007).

8.4.2 PARTIAL RESPONSE

Partial response (PR) is defined as the regression of measurable disease and no new sites of disease. Regression is defined as greater than or equal to 50% decrease in the sum of the products of the diameters (SPD) of the index lesions, coupled with no unequivocal increase in size of other lymph nodes, liver or spleen. No new sites of disease should be observed. In subjects with FDG-avid lymphoma with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site. For subjects with variably

FDG-avid lymphomas or where FDG-avidity is unknown, if no pretreatment PET scan is available, or if a pretreatment PET scan was negative, CT criteria should be used. If bone marrow was involved prior to therapy and a clinical CR was achieved but no bone marrow assessment is completed after treatment then these subjects are considered partial responders (Cheson et al., 2007).

8.4.3 STABLE DISEASE

Stable disease is defined as the failure to attain CR/PR but does not fulfill the criteria for progressive disease. For subjects with FDG-avid lymphomas, the PET scan should be positive at prior sites of disease and there should be no new areas of involvement. For those with disease evaluated by CT only, there must be no unequivocal change in the size of the previous lesions on the post-treatment CT scan (Cheson et al., 2007).

8.4.4 PROGRESSION OF DISEASE

Any of the following conditions will constitute relapsed or progressive disease:

Appearance of any new lesion more than 1.5 cm in any axis, even if other lesions are decreasing in size will be considered relapsed or progressive disease. Increase in FDG uptake in a previously unaffected site should be confirmed with other modalities, a therapeutic decision should not be made solely on the basis of PET without histologic confirmation (Cheson et al., 2007).

There is at least a 50% increase from nadir in one of the following:

- The SPD of index lesions,
- The greatest transverse diameter (GTD) of any individual previously involved node, or
- The GTD of any previously involved node provided that the GTD of that node is now ≥ 1.5 cm.

Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT) (Cheson et al., 2007).

8.5 DEFINITIONS OF DISEASE PARAMETERS

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least two dimensions with conventional techniques (CT, PET/CT, MRI, x-ray) and meet one of the following criteria: nodal lesion with a long axis > 1.5 cm regardless of short axis, nodal lesion with long and short axes ≥ 1.0 cm, or extranodal lesions with long and short axes ≥ 1.0 cm with spiral CT scan. All tumor measurements should be recorded in centimeters.

Non-measurable disease (evaluable disease): All other lesions (or sites of disease) including small lesions, (< 1.0 cm using spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, and cystic lesions are all non-measurable.

Index lesions: All measurable lesions up to a maximum of 6 nodal and extranodal lesions total, representative of all involved organs, should be identified as **index lesions** and recorded and measured at baseline. Index lesions should be selected on the basis of their size (clearly measurable in two perpendicular dimensions), and the highest FDG avidity (high SUV lesions may be prioritized even if not the largest lesions, and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A baseline sum of product of the diameters (SPD) for all index lesions will be calculated and reported as the baseline SPD. The baseline SPD will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-index lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 6 index lesions should be identified as **non-index lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.6 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria as per the NHL established criteria used in this study (See Appendix A).

8.6.1 DURATION OF RESPONSE

Duration of response is defined as the time from documentation of a response to treatment to the first documentation of tumor progression or death due to any cause whichever comes first. Duration of the response will be summarized using n (sample size), mean, standard deviation, median, minimum, and maximum for the responders.

Duration of stable disease:

Stable disease is measured from the start of the treatment until the criteria for progression are met.

Progression-Free Survival:

Progression free survival (PFS) is defined as the time from study entry to the first documentation of tumor progression or death due to any cause whichever comes first. This variable will be analyzed via Kaplan-Meier methodology. The median PFS will be estimated.

9 STATISTICAL CONSIDERATIONS

The sections of the Statistical Considerations describe the statistical methods to be used to analyze the efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how censoring procedures will be applied to time to event related variables as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

9.1 SAMPLE SIZE AND POWER

[redacted]

9.2 GENERAL ANALYSIS CONVENTION

This is an open-label, Phase 2, study of the PI3K delta inhibitor umbralisib in combination with ublituximab. This trial is designed to evaluate the overall response rate (CR + PR), as well as duration of response (DOR), complete response (CR), and progression-free survival (PFS) in treatment naïve follicular lymphoma and small lymphocytic lymphoma subjects. Assessment of lymphoma response (CR, PR or SD) and disease progression will be evaluated as outlined in the schedule of assessments (Section 5), according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007). Subjects who progress according to the corresponding criteria will receive no further treatment. Subjects who respond to the treatment (i.e., CR, PR or SD) may remain on trial.

Safety will be examined on an ongoing basis while the study is being conducted. Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE).

Unless otherwise stated, all analyses will be performed using SAS Version 9.4 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 subjects who provide some efficacy assessments and the safety population will include all subjects 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 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized using descriptive statistics for continuous variables, and frequencies and percentages for categorical variables.

9.5 MEDICAL HISTORY

Medical history will be captured at the Screening visit. Medical history will be coded using MedDRA and will be summarized by MedDRA system organ class and preferred term for the Safety population.

9.6 EXTENT OF EXPOSURE

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

9.7 EFFICACY ANALYSES

Two populations will be used in the efficacy analyses, Intent-to-Treat (ITT) and Per Protocol (PP) populations. The ITT population will include all safety population who provide efficacy assessment, and PP population will include all ITT population without major protocol violations.

The efficacy endpoints will include:

- Overall response rate (ORR)
- Complete response (CR)
- Duration of Response (DoR)
- Progression-free Survival (PFS)

These variables will be analyzed/summarized based on the ITT population as well as the PP population as appropriate. The percentages of CR, CR+PR, and CR+PR+SD will be presented, as will the median duration of response. The lower bound of these percentages will be presented using the Clopper-Pearson Exact method to estimate the 95% confidence interval.

Additional analyses may also be performed as appropriate

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 - ORR

Overall Response Rate (ORR) will be determined per the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007). Overall Response Rate (ORR), is defined as percent of subjects who achieve CR or PR. We will estimate 95% confidence intervals for the response rates. These will be followed by additional logistic regression analyses model to adjust for demographic and baseline parameters.

9.9.2 SECONDARY EFFICACY OUTCOMES

Secondary efficacy outcomes will include:

- Progression-free Survival (PFS), Complete Response (CR) and Duration of Response (DOR)

9.9.2.1 PROGRESSION-FREE SURVIVAL

Progression-free survival (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. PFS will be presented using the 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.

Hypothesis testing for pairwise comparison will be performed using a log rank test via SAS Lifetest procedures. The median duration of PFS and the proportion of subjects alive and progression-free at 6, 12, and 18 months will be estimated using the Kaplan-Meier method. For each estimate, a 95% confidence interval will be reported.

9.9.2.2 CR RATE

CR rate is defined as the percent of subjects who achieve a CR. CR rate will be analyzed via chi square test. The 95% confidence intervals for the response rates as well as for the differences of the complete
response rate will be presented. Additional logistic analyses model may be used to assess the impact of demographic and baseline parameters.

9.9.2.3 DURATION OF RESPONSE

Duration of response (DOR) 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. This variable will be summarized. Estimates of median DOR will be made using Kaplan-Meier methods.

[redacted]

10 SAFETY REPORTING AND ANALYSIS

10.1 SAFETY ANALYSES

The safety population will include all subjects who received any study medication. The safety endpoints will include:

- Incidence of AEs and AEs considered to be drug-related
- Incidence of Grade 3 and Grade 4 AEs
- Incidence of SAEs
- Laboratory values

The safety endpoints will be listed and/or summarized. No inferential statistical analyses will be performed. All subjects who have received at least one dose of ublituximab and/or umbralisib will be included in the safety population.

The analyses of safety will be based on the frequency of adverse events and their severity for subjects in each portion who received at least one dose of study treatment. Worst toxicity grades per subject will be tabulated for select adverse events and laboratory measurements by using NCI CTCAE criteria v4.0.

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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 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 ublituximab and TGR-1202 Investigator Brochures.

10.3 DEFINITIONS OF ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject 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.

10.4 ADVERSE EVENTS (AE'S) AND TREATMENT EMERGENT ADVERSE EVENTS (TEAE'S)

All AEs and SAEs occurring on study will be listed by subject. The frequency and percentages of subjects with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term (PT), where treatment-emergent is defined as any AE that:

- Occurs after first dosing of study medication 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.

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

AEs that occur after informed consent but before first dosing of study medication will not be summarized but will be listed.

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

10.5 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.

10.5.1 RECORDING OF ADVERSE EVENTS

All adverse events of any subject during the course of the study will be reported on the case report form, and 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 drugs administration – umbralisib and/or ublituximab). If the adverse event is serious, it should be reported as soon as possible and no greater than 24 hours to the sponsor or designee. 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 and/or ublituximab treatment spanning from Cycle 1/Day 1 until 30 calendar days after discontinuation or completion of either protocol-specific treatment as defined by the protocol for that subject, are to be recorded on the eCRF.

10.5.2 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 subject to discontinue study treatment, or the investigator insists that the abnormality should be reported as an AE. Abnormal laboratory results should be noted in the eCRF 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 that must be collected in the relevant eCRF. If the lab abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE 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. Subjects with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized, and graded per NCI CTCAE Version 4.0 when applicable. Subject incidence of abnormal lab results will be summarized by treatment group and maximum grade for each abnormal lab finding.

10.5.3 HANDLING OF ADVERSE EVENTS

All adverse events resulting in discontinuation from the study should be followed until resolution or stabilization. Subjects should be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment (umbralisib or ublituximab). 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 subject's medical record and as a comment on the eCRF. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

10.6 SERIOUS ADVERSE EVENTS

10.6.1 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 subject 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 Cheson et al. 2007, 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(s) 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
- Admission for study related treatment

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 to the Sponsor.

10.6.2 SERIOUS ADVERSE EVENT REPORTING BY INVESTIGATORS

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 on the eCRF.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to the Sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time after signing of informed conmsent through the 30-day follow-up period after the last study treatment. Sponsor or designee 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.

To report an SAE, see the appropriate form.

All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to the sponsor as SAEs within the CRF and followed until resolution (with autopsy report if applicable).

Disease progression or death due to disease progression should be reported by the investigator as a serious adverse event only if it is assessed that the study drugs caused or contributed to the disease progression (i.e. by a means other than lack of effect). Unrelated events of disease progression should be captured on the appropriate eCRF.

The investigator must review and sign off on the SAE data on the SAE report. The SAE should be reported to the Sponsor (or Sponsor designee) as outlined in the Safety Monitoring Plan.

When an SAE is reported to the sponsor or designee, the same information should be entered on the eCRF within 24 hours (1 business day). 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 the sponsor or designee as soon as it is available; these reports should be submitted using the appropriate SAE form.

Investigators must report SAEs 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 SPONSOR SAE REPORTING REQUIREMENTS

Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

Sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. The Sponsor 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 regulatory agencies and competent authorities by a written safety report within 15 calendar days of notification. Following the submission to the regulatory agencies and competent authorities, Investigators and trial sites will be notified of the SUSAR. Investigators must report 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).

10.8 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 AE eCRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE eCRF; AEs that meet the definition of an SAE should additionally be reported.

10.9 DIAGNOSIS VS. SIGNS AND SYMPTOMS

All AEs should be recorded individually in the subject'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) (SAE Report Form and/or AE eCRF). 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.

10.9.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF. 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 AE eCRF.

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

10.9.2 ABNORMAL LABORATORY VALUES

Abnormal laboratory results should be noted in the eCRF 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 that must be collected in the relevant eCRF. 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.

10.9.3 DEATHS

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of the subject's disease for up to 30 days post the last dose of study drug will be recorded on the appropriate study eCRF and reported on the Adverse Event page of the eCRF, i.e. are exempted from expedited reporting. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sponsor.

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 as the single medical concept on the Adverse Event page of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event page.

10.9.4 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 10.6.1.

10.9.5 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 on the study's appropriate medical history eCRF. 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 AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

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

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

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

If a subject becomes pregnant while enrolled in the study, an SAE form should be completed and submitted to the Sponsor. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor.

Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting.

Study Drug Overdose

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

Secondary/Second Primary Malignancy

Any secondary malignancy or second malignancy event must be reported via the SAE form (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 SITE MONITORING PLAN

A Sponsor representative or designee will have made a site visit to each institution within 12 months prior to initiating the protocol to inspect the drug storage area, and fully inform the Investigator of his/her responsibilities for studies and the procedures for assuring adequate and correct documentation.

A study initiation site visit, a teleconference and/or a planned investigator meeting will be performed to review investigator responsibilities and protocol requirements. During the initiation, the electronic case report forms (eCRFs) and other pertinent study materials will be reviewed with the investigator's research staff. During the course of the study, the Sponsor will make visits to the sites as necessary in order to review protocol compliance, examine eCRFs, and individual subject medical records, and ensure that the study is being conducted according to the protocol and pertinent regulatory requirements. Selected eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that subject confidentiality is maintained.

Site monitoring shall be conducted to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

11.2 AMENDMENTS TO THE PROTOCOL

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of the Sponsor and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to subject, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and specifically when an increase to dosing or subject exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and Ethics Committee and/or FDA and Competent Authority approval may include the following:

- Change to study design

- Risk to subject
- Increase to dose or subject exposure to drug
- Subject number increase of more than 20%
- Addition or removal of tests and/or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the subjects, their consent to continue participation in the study should be obtained.

11.3 CURRICULA VITAE AND FINANCIAL DISCLOSURES

All Principal Investigators will be required to submit to the Sponsor or its designee an up-to-date signed curriculum vitae (CV), current within two years, a current copy of their medical license, and a completed FDA form 1572 and financial disclosure statement. In addition, all sub-investigators will be required to submit to the Sponsor or its designee an up-to-date signed CV, current within two years, a current copy of their medical license, and a completed financial disclosure statement.

11.4 DATA OWNERSHIP AND PUBLICATION

By conducting this study, the Investigator affirms to Sponsor that he or she will maintain, in strict confidence, information furnished by the Sponsor including data generated from this study and preliminary laboratory results, except as exempted for regulatory purposes.

All data generated during the conduct of this study is owned by the Sponsor and may not be used by the Investigator or affiliates without the expressed written consent of the Sponsor.

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

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, IB, available safety information, subject documents (e.g., study diary), subject recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the subjects and documentation evidencing the PI's qualifications must be submitted to the IRB for ethical review and approval prior to the study start.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB study review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

If applicable, the PI will notify the IRB **within 90 days** of the end of the study, or if the study terminates early, the PI must notify the IRB **within 15 days** of the termination. A reason for the early termination must be provided (as defined in Directive 2001/20/EC). The Sponsor will either prepare or review all submission documents prior to submission to the IRB.

12.2 REGULATORY APPROVAL

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

Safety updates for ublituximab and/or umbralisib will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

12.3 INSURANCE AND INDEMNITY

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

12.4 INFORMED CONSENT

Informed consent is a process by which a subject 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 subject'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. Each consent form must include all of the relevant elements currently required by the responsible regulatory authority, as well as local county authority or state regulations and national requirements.

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 subject's medical record. A copy of the informed consent form, to include the subject's signature, will be provided by the investigator to the subject.

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

12.5 CONFIDENTIALITY

Subject Confidentiality

Confidentiality of subject'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, a subject must sign an authorization from the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from subjects 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 subject's medical records, but the subject 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 subject to revoke his or her authorization.

In the event that a subject 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 subject authorization. For subjects 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 subject 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 the Sponsor, the regulatory authorities and the IRB direct access to review the subject's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify subjects on the eCRF or other documents submitted to the Sponsor. This information, together with the subject's date of birth, will be used in the database for subject identification. Subject names or addresses will not be entered in the eCRF or database. No material bearing a subject's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

12.6 INVESTIGATOR AND STAFF INFORMATION

Personal data of the investigators and sub-investigators may be included in the Sponsor database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

12.7 FINANCIAL INFORMATION

The finances for this study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

13 RECORD RETENTION AND DOCUMENTATION OF THE STUDY

13.1 DOCUMENTATION REQUIRED TO INITIATE STUDY

Before the study may begin, documentation required by FDA regulations and/or local regulatory authorities must be provided by the Investigator. The required documentation should be submitted to the Sponsor.

Documents at a minimum required to begin the study include, but are not limited to, the following:

- A signature-authorized protocol and contract;
- A copy of the official IRB approval of the study and the IRB members list;
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study;
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory;
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed;
- A copy of the IRB-approved consent form containing permission for audit by representatives of the Sponsor, the IRB, and the FDA;
- Financial disclosure forms for all investigators listed on Form FDA 1572;
- GCP Certificate for study training;
- Site qualification reports, where applicable;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

The Sponsor/Sponsor designee will ensure that all documentation that is required to be in place before the study may start, in accordance with ICH E6 and Sponsor SOPs, will be available before any study sites are initiated.

13.2 STUDY DOCUMENTATION AND STORAGE

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the subject's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, EKG traces, copies or

transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and study staff are responsible for maintaining a comprehensive and centralized filing system (Site Study File/SSF or ISF) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 13 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, IRB approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating subjects (sufficient information to link records e.g., medical records), all original, signed informed consent forms, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representative will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, either the Sponsor or its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to sponsor. The investigator must obtain the sponsor written permission before disposing of any records, even if

retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study, and will be transferred to the Sponsor at the conclusion of the study.

13.3 DATA COLLECTION

The study eCRF is the primary data collection instrument for the study. An electronic case report form will be utilized for the collection of all data and all data will be entered using the English language and should be kept current to enable the monitor to review the subjects' status throughout the course of the study.

In order to maintain confidentiality, only study number, subject number, initials and date of birth will identify the subject in the eCRF. If the subject's name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the investigator site and replaced instead with the subject number and subject's initials. The investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

13.4 STUDY MONITORING, AUDITING, AND INSPECTING

The investigator will permit study-related monitoring, quality audits, and inspections by government regulatory authorities, the Sponsor or its representative(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or QA reviewer is given access to all study-related documents and study-related facilities.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities and the sponsor or its representative(s).

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

13.5 QUALITY ASSURANCE AND QUALITY CONTROL

In addition to the Clinical Monitoring component of this protocol, the Sponsor's Quality Assurance (QA) department shall establish an Auditing Plan document separate from the protocol to establish the criteria by which independent auditing shall be conducted during the conduct of the study to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

Each study site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for study conduct, data generation & collection, recording of

data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

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

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

13.6 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study.

A clinical study report will be prepared upon completion of the study. The Sponsor will disclose the study results, in the form of a clinical study report synopsis, to the IEC and the applicable regulatory authorities within one year of the end of the study. The format of this synopsis and that of the clinical study report and its addendum will comply with ICH E3 guidelines for structure and content of a clinical study report.

The financial disclosure information will be provided to the Sponsor prior to study participation from all PIs and Sub-Investigators who are involved in the study and named on the FDA 1572 form.

By conducting this study, the Investigator affirms to the Sponsor that he or she will maintain, in strict confidence, information furnished by the Sponsor including data generated from this study and preliminary laboratory results, except as exempted for regulatory purposes.

All data generated during the conduct of this study is owned by the Sponsor and may not be used by the Investigator or affiliates without the expressed written consent of the Sponsor.

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

14 REFERENCES

Altekruse SF, K. C. (2010, November). *SEER Cancer Statistics Review*. Retrieved from seer.cancer.gov: http://seer.cancer.gov/csr/1975.2007

American Cancer Society. (2015). *American Cancer Society.* Retrieved June 5, 2015, from www.cancer.org: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf

Cazin B, L. S. (2013). Final results of a multicenter phase Ib single agent study with the novel anti-CD20 monoclonal antibody ublituximab (TG-1101) in patients with relapsed chronic lymphocytic leukemia (CLL). *European Hematology Assocation*, (p. abstractP111). Stockholm.

Cheson, B. D., Pfistner, B., Juweid, M. E., Gascoyne, R. D., Specht, L., Horning, S. J., . . . Diehl, V. (2007). Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology, 25*(5), 579-586. doi: 10.1200/JCO.2006.09.2403

Cheson, B.C., Fisher, R.I., Barrington, S.F., Cavalli, F., Schwartz, L.H., Zucca, E., Lister, T.A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology,* 32, (1-10). doi: 10.1200/JCO.2013.54.8900

de Romeuf C, D. C.-T.-B. (2008). Chronic lymphocytic leukaemia cells are effeciently killed by an anti-CD20 monoclonal antibody selected for improved engagement of FcgammaRIIIA/CD16. *British Journal of Haematology, 6*(140), 635-643.

Esteves IT, D. C. (2011). LFB-R603 (ublituximab), a third-generation monoclonal anti-CD20 antibody, displays additive antitumor activity with antileukemic chemotherpeutic agents in mouse xenograft models. *American Society of Hematology*, abstract 1660.

Genentech Inc. (2013, September). Rituxan (rituximab) Prescribing Information. South San Francisco, CA.

Hallek M, C. B.-C. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Wrokshop on Chronic Lymphocytic Leukemia updating the National Cancer Institue - Wroking Group 1996 Guidelines. *blood, 12*(111), 5446-5456.

Lin K, S. P. (2002). Relationship between p53 dysfunction, CD38 expression and IgVH mutatin in chronic lymphcytic leukemia. *blood*, 1404.

Lunning M, Vose J, Fowler N, Nastoupil L.....O'Brien S. (2015). Ublituximab + TGR-1202 demonstrates activity and a favorable safety profile in relapsed/refractory B-cell NHL and high-risk CLL: Phase I Results. *ASCO Annual Meeting and Exposition*, Orlando, FL.

O'Connor OA, D. C. (2014). A phase I trial of ublituximab (TG-1101), a novel anti-CD20 monoclonal antibody (MAB) in B-cell lymphoma patients with prior exposure to rituximab. *American Society of Clinical Oncology*, (p. abstract 8524). Chicago.

[redacted] (2011). *PI3Kgamma enzyme assay.* Shameerpet, India: Incozen Therapeutics.

[redacted] (2011). *AKT phosphorylation in MOLT-4 cells. June Study Report IVT-5264-APM-10.* Shameerpet, India: Incozen Therapeuticis PVT Ltd.

[redacted] (2011). *AKT phosphorylation in THP-1 cells. Study Report IVT-5264-ATP-08.* Shameerpet, India: Incozen Therapeuticis PVT Ltd.

Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, Au WY, et al. Follicular Lymphoma International Prognostic Index. Blood. 2004; (104)5: 1258-65.

Therapeutics, T. (2017). Ublituximab (TG-1101) and TGR-1202 Investigator's Brochure (Vol. Version 5.0).

15 APPENDIX A – ECOG PERFORMANCE STATUS SCALE

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

16 APPENDIX B - CONTRACEPTION 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 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 effective contraception during the study and for 4 months after the last dose of either study treatment. Effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. 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 subjects on the study, the vasectomised male partner should be the sole partner for that subject.
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 ≤ 72 hours prior to initiating treatment.

Fertile Males

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment and for 4 months after the last dose of either study treatment. They should also not father a child during this period.

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to TG Therapeutics Inc. within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the 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 should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to TG Therapeutics Inc. 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 on the SAE Report Form.

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.

17 APPENDIX C – NEW YORK HEART ASSOCIATION 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.

18 APPENDIX D – INTERNATIONAL WORKING GROUP REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA (CHESON ET AL. 2007)

Complete Response (CR):		*The designation of CR requires the following:* • Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before herapy. • Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. • Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment. • The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma. • If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Complete Response/Unconfirmed (CRu):	*The use of the above definition for CR and those below for PR eliminates the category of CRu.*

Partial Response (PR):	*The designation of PR requires all of the following:* • At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved. • No increase should be observed in the size of other nodes, liver, or spleen. • Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter. • With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present. • Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders. • No new sites of disease should be observed. • Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site. • Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. *In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual*

	lesions are unlikely to be PET negative and should be considered partial responders.
Stable Disease (SD):	*Stable disease (SD) is defined as the following:* • A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]). • Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET. • Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.
Relapsed Disease (after CR) / Progressive Disease (after PR, SD):	*Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.* • Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation. • At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis. • At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis. • Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g.,

pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Response Assessment:

Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	• FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative • Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	• ≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes • FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site • Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified

Response Definitions for Clinical Trials (continued)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
SD	Failure to attain CR/PR or PD	• FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • Variably FDG-avid or PET negative; no change in size of previous lesions on CT	—	—
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis • Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Source: Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol. 2007;25(5):579-86.

19 APPENDIX E – FOLLICULAR LYMPHOMA STAGING AND FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

Ann Arbor Staging

Stage	Area of Involvement
I	Single lymph node region
II	Involvement of ≥ 2 lymph node regions on the same side of the diaphram
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of ≥ 1 extra-lymphatic organs with or without lymph node involvement
X	Bulky disease, defined as one or more site of disease of > 10 cm diameter, or mediastinal widening to > 1/3 of chest width on chest x-ray

FLIPI

Classification	Number of Factors
Low risk	0-1 risk factor
Intermediate risk	2 risk factors
High risk	≥3 risk factors
Parameter	**Adverse Factor**
Age	≥ 60 y
Ann Arbor stage	III-IV
Hemoglobin level	< 120 g/L
Serum LDH level	ULN
Number of nodal sites	> 4

Source: Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, Au WY, et al. Follicular Lymphoma International Prognostic Index. Blood. 2004; (104)5: 1258-65.

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

CDC

www.cdc.gov/hepatitis