Ublituximab as initial therapy for treatment-naive follicular or marginal zone lymphoma with response-driven addition of umbralisib for suboptimal response

Protocol Number:	**18-2128**
Principal Investigator:	**Manali Kamdar, MD, MBBS**
IND/IDE:	**149590**
Coordinating Center/Sponsor and Lead Principal Investigator/Sponsor-Investigator:	**University of Colorado, Manali Kamdar**
Funded by:	**TG Therapeutics, Inc., (Tracking Number: U2-NTG-009)**
Version Date:	**Version 7.0, Dated May 17, 2021**

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Manali Kamdar, MD, is conducting the study. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
ADCC	Antibody-dependent cytotoxicity
AE	Adverse Event
ATP	Acure thrombocytopenic purpura
CDC	Complement-Dependent Cytotoxicity
CFR	Code of Federal Regulations
CLL	Chronic Lymphocytic Leukemia
COMIRB	Colorado Multiple Institutional Review Board
CR	Complete response
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ENMZL	Extra-nodal marginal zone lymphoma
EoT	End of therapy
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index)
GELF	Groupe d'Etude Lymphomes Folliculaires
ITT	Intent-to-treat
HIPAA	Health Insurance Portability and Accountability Act
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NOAEL	No-observed-adverse-effect-level
ORR	Overall Response Rate
OS	Overall Survival
PCD	Programmed cell death
PD	Progressive disease
PET/CT	Positron Emission Tomography/computerized tomography
PFS	Progression-Free Survival
PJP	*Pneumocystis jiroveci* pneumonia
PR	Partial response
QC	Quality Control
QD	Once a day
QoL	Quality of Life
R	Rituximab
RT	Radiation therapy
SAE	Serious Adverse Event

SD	Stable disease
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
TGT	TG Therapeutics, Inc.
U2	Ublituximab + Umbralisib
UAP	Unanticipated Problem
Ub	Ublituximab
Um	Umbralisib

PROTOCOL SYNOPSIS

Protocol Title: *Ublituximab as initial therapy for treatment-naive follicular or marginal zone lymphoma with response-driven addition of umbralisib for suboptimal response*

Objectives:

Primary Objectives:

To determine Best Complete response (CR) rates at anytime during treatment with single agent or combination therapy

Secondary Objectives:

- To determine Overall response rates (ORR) in the entire cohort
- To assess safety and tolerability profile of single agent and combination therapy

Exploratory Objectives

- To determine ORR and CR rates after induction therapy in FL (Follicular lymphoma) and MZL (Marginal Zone Lymphoma) cohorts
- To determine ORR and CR rates after combination therapy in the entire FL and MZL cohorts
- To determine Partial response (PR), Stable disease (SD), progressive disease (PD) rate of single agent and combination therapy
- To assess duration of remission of single agent and combination therapy
- To assess 2-yr progression free survival (PFS) and overall survival (OS) of single agent and combination therapy

- To explore baseline disease and patient factors that may predict response to ublituximab alone and with umbralisib.
- To assess rates of transformation to aggressive lymphoma
- To evaluate the health-related quality of life (QoL) of subjects as assessed by the following subject-reported questionnaire
  - FACT-Lym, a standardized instrument for use as a measure of health-related QoL as highlighted in the **APPENDIX** section
- Correlative analysis: M7FLIPI testing at diagnosis may be performed which can help predict CR rates with single versus combination therapy. Patient samples will be tested in a CAP/CLIA-accredited laboratory on a custom next generation sequencing (NGS) panel. This panel consists of 310 genes, which are recurrently mutated across clonal hematopoietic proliferations including clonal hematopoiesis of indeterminate potential (CHIP), acute and chronic myeloid neoplasms, B- and T-cell lymphomas, and plasma cell neoplasms. Specifically included in this panel are the full coding sequences of the seven genes in the m7-FLIPI clinopathologic riskmodel: *ARID1A*, *CARD11*, *CREBBP*, *EP300*, *EZH2*, *FOXO1*, and *MEF2B*. (Pastore et al. Lancet Oncol 2015).[10] Mutation data will be analyzed by a board-certified molecular pathologist and these results will be incorporated with clinical data to determine the m7-FLIPI score.
- Minimal residual disease assessment may be performed on patient samples

Endpoint:

Primary Endpoints:

- Best Complete response (CR) rates at any timeanytime during treatment with single agent or combination therapy as defined by the Lugano response Criteria for NHL (Cheson 2014)

Secondary Endpoints:

- To determine Overall response rates (ORR) in the entire cohort as defined by the Lugano response Criteria for NHL (Cheson 2014)
- Ublituximab tolerability as per CTCAE V5.0 criteria
- Umbralisib tolerability as per CTCAE V5.0 criteria

Population:

- **Sample size**
  - Maximum number of participants that can be screened is 30 (will allow for up to 20% screen failures/drop-out rate). 24 patients are required for this study.
- **Gender** Male or Female
- **Age Range** ≥ 18years
- **Demographic group** Any
- **General health status** ECOG 0-2
- **Geographic location** Participating medical center

Phase: II

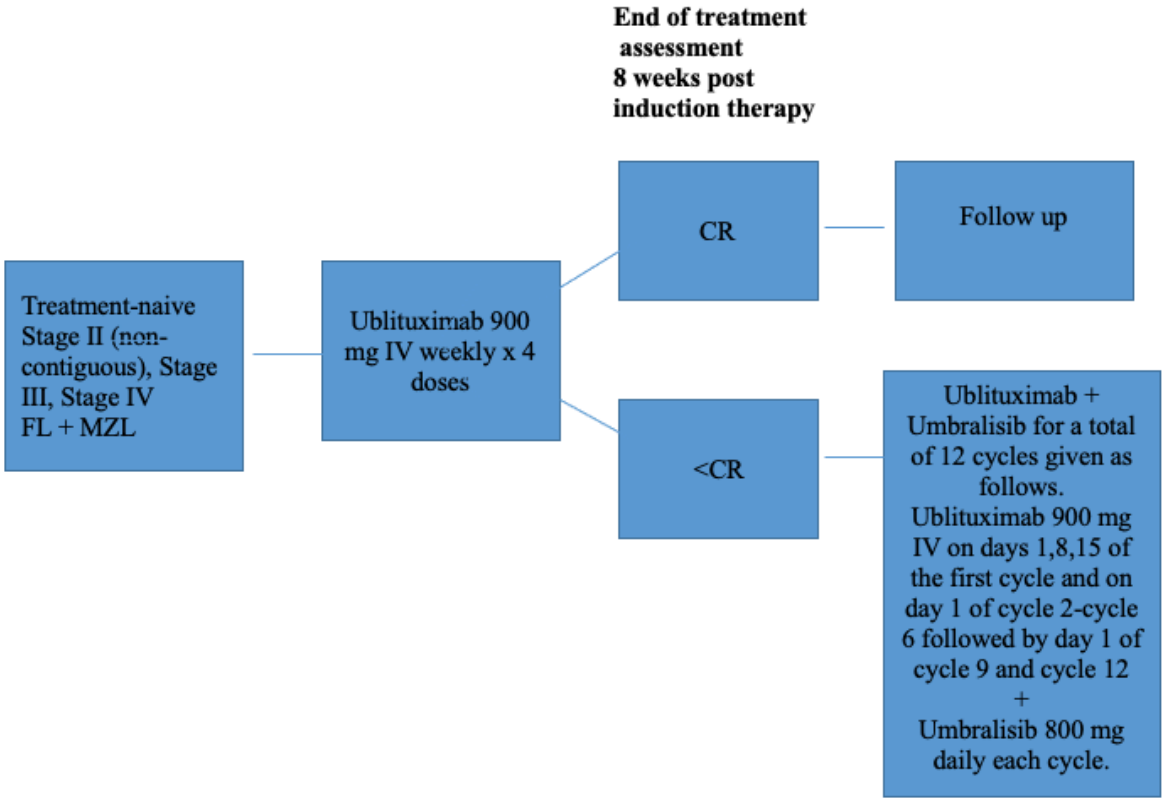
Number of Participating Sites enrolling participants: 1

Description of Study Agent: AntiCD20 antibody and PI3K inhibitor

Study Duration: Patient enrollment is expected to last for 2 years. Patients will be followed for outcome measures for up to 2 years after enrollment in study.

After last patient has completed end of Treatment (EOT) assessment, results will be analyzed and published.

SCHEMATIC OF STUDY DESIGN



1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND INFORMATION

1.1.1 INDOLENT NON-HODGKIN (FOLLICULAR AND MARGINAL ZONE LYMPHOMA): CURRENT LANDSCAPE AND CHALLENGES

Non-Hodgkin lymphoma (NHL) is the seventh most common cancer and the sixth leading cause of cancer deaths in the United Stated. NHL is further subdivided into aggressive and indolent lymphomas. Indolent lymphomas are slow growing, chronic, treatable, frequently relapsing cancers which are considered incurable with currently available therapies.[1] Thus, the psychological and socio-economic burden of these indolent lymphomas is enormous to patients and healthcare facilities.

Follicular lymphoma (FL) is the most common indolent NHL in the western hemisphere.[2] FL is characterized by an indolent clinical course, typical morphology, and the presence of a chromosomal translocation, t(14;18)(q32;q21) or a variant pattern in 85% of patients which results in the overexpression of BCL-2 protein, a member of the family of proteins that blocks apoptosis.[3] Based on the proportion of centrocytes to centroblasts, FL is further divided into 3 grades: Grade 1, Grade 2, Grade 3A and Grade 3B with evidence suggesting that Grade 1-3A are biologically indolent whereas Grade 3B has an aggressive clinical course similar to diffuse large cell lymphoma.[4,5] FL represents significant heterogeneity, with some patients not requiring therapy for several years after diagnosis or achieving long remissions with initial treatment, while other patients needing immediate therapy at diagnosis and relapse within a short time or are refractory to treatment, resulting in shortened survival. Additionally, approximately 30% of FL patients will transform to a more aggressive histology during their disease course, often leading to rapid progression and the need for intensive therapy.[6]

In newly diagnosed FL, there are multiple clinical factors prognostic of outcome including age, LDH (Lactose Dehydrogenase), β2-microglobulin, disease bulk, and stage of disease which have been used to develop prognostic tools such as the FLIPI (Follicular Lymphoma International Prognostic Index), FLIPI2, and guidelines to assist in making treatment decisions such as the GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria [7]. In addition, newer markers such as response by positron emission tomography/computerized tomography (PET-CT), minimal residual disease (MRD) and biomarkers like m7-FLIPI have been recognized to correlate with disease outcome.[8,9,10]

The present day approach outlined in the NCCN (National comprehensive cancer network) guidelines is based on stage and burden of FL. Recommendations listed in the NCCN guidelines for early-stage FL (Stage I-II) range from watchful waiting, radiation therapy to single-agent rituximab. Based on Lymphocare database, comparable outcomes have been found with either of

these approaches.[11] However, none of these strategies have been compared head-to head in a prospective setting.

The NCCN guidelines for patients with advanced-stage disease are based on disease burden (i.e. low tumor burden versus high tumor burden). Patients with low tumor burden FL are most often observed with a watch-and-wait approach[12] or treated with single-agent rituximab.[13] Patients with high tumor burden FL are most often treated with combination chemoimmunotherapy (R-chemotherapy), lenalidomide plus rituximab, single agent rituximab with the possibility of rituximab maintenance. [14-16]

FL is considered an incurable disease in the majority of patients with currently available therapeutic options. For several years it appeared that the overall survival of low grade FL was around 10 years or under[17] and that it might not be significantly affected by therapy. However, more recent studies in the era of antiCD20 monoclonal antibodies have suggested a significant improvement in overall survival now almost approaching 20 years.[18,19] Overall survival of patients with FL grade 1 or 2 treated by physicians in the Nebraska lymphoma group between 1982 and 2014 suggested that patients treated before the advent of monoclonal antibodies experienced a decreased overall survival compared to patients treated after.[20]

In order to improve overall outcomes of patients with FL it is important to identify risk-groups, which would derive most benefit from novel therapeutic approaches. NCI (National Cancer Institute) Lymphoma Clinical Trials Planning Meeting Follicular Subcommittee thus identified two populations of patients who are thought to be the highest priority for further study. The first patient population pertains to patients with high-risk disease. The second population of FL patients recommended for study is "watch and wait" group, or those considered low risk. In order to assure that these patients are similar at diagnosis, the use of the GELF criteria is recommended to identify low-risk patients who are appropriate for observation. There are several trials currently ongoing that focus on high-risk groups with novel therapeutic interventions. However, very few to none are focused on low tumor burden FL patients.[21] Studies in FL take decades, and most of the studies suggesting no impact on survival in delaying therapy were done before the availability of monoclonal antibodies. Studies done in the era of monoclonal antibodies are few with a shorter follow up. The fact that there is no proof that delaying therapy does not decrease survival does not rule out the possibility that it could be true. We believe that in order to gain a better understanding of the natural history and biology of follicular lymphoma, it will also be important to study the "low-risk" group of patients as well.

Another subset of indolent lymphomas called marginal zone lymphoma (MZL) is the third most common lymphoma, accounting for 8-12% of all B-cell NHL. MZL is an indolent malignancy with three main subtypes of varying frequency: Extra-Nodal MZL of the mucosa-associated lymphoid tissue (ENMZL) (70%); splenic MZL (SMZL) (20%); and nodal MZL (NMZL) (10%).[22] ENMZL typically presents with localized disease whereas SMZL and NMZL present with disseminated disease. In the absence of standard treatment of both SMZL and NMZL, current treatment strategies for low tumor burden patients recommend watchful waiting or single agent rituximab therapy.[23] In fact, the NCCN guidelines currently suggest therapy for NMZL and advanced MZL to be similar to FL patients. Thus this subtype of lymphoma continues to be understudied and poorly represented in clinical trials.

Rituximab, an anti-CD20 antibody therapy, is commonly used as single agent for the treatment of FL and MZL.[1] In patients with FL, single agent rituximab yields an overall response rate (ORR) of 77% and a complete response rate (CR) of 36%.[24] In patients with MZL, single agent rituximab has shown to yield an ORR of 52% and a CR of 12%. There have been few clinical trials focusing on subtypes of MZL. However, existing data shows that the use of single agent rituximab in NMZL can achieve an ORR 60% and a CR 35%.[25] In ENMZL single agent rituximab has shown to achieve an ORR 73% CR 44%[26] whereas in SMZL single agent rituximab has shown to yield an ORR of 90% and a CR rate of 50%.[27] Based on these responses, it is clear that there is ample scope to improve and deepen these responses by implementing novel therapeutics.

In patients with FL and MZL who achieve a partial response (PR) or stable disease (SD) to single agent rituximab induction therapy, no data currently exists to guide further management. Most treatment centers either implement a "watchful waiting" strategy for clinically asymptomatic patients while others recommend extended duration rituximab.[25] It is intuitive that these patients who do not achieve a CR are bound to have progressive disease earlier in their disease course thus potentially impacting outcomes adversely. This subset of patients has rarely been studied in clinical trials and thus continues to be an unmet need.

1.1.2 NOVEL THERAPEUTICS

a. 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 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).

Pre-Clinical Development of Ublituximab

In Vitro Activity

In an in-vitro assay using B-CLL cells from patient donors, ublituximab demonstrated an enhanced ability to kill CLL (chronic lymphocytic leukemia) 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 patient-derived CLL cells and NHL cell lines. Ublituximab's engagement

to FcγRIIIA triggers a stronger natural killer (NK) cell cytotoxicity against CLL as compared to rituxan (in vitro) despite CD20 density, likely related to the glycosylation pattern (de Romeuf C, 2008).

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.[28]

Clinical Development of Ublituximab

Ublituximab has been studied in a variety of patient populations, both as a single agent, and in combination with other agents, with over 1,000 patients 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 patients. 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 patients 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.

In a two part, first-in human dose escalation study (protocol CD20-0703), patients 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 that used an initial dose of 150 mg followed by 7 doses of 450 mg (total dose 3300 mg). Median time from diagnosis to inclusion was 10.4 years [4.0–23.6] and median prior therapies was 3 [1–8]. Seven patients (58%) received at least one prior rituximab-containing regimen. The most frequent drug-related adverse events (AEs) reported were infusion related reactions (IRR) (75% of the patients, including 33% of patients with Grade 3 IRR). Other Grade 3/4 AEs > 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. Therefore, the maximum tolerated dose was not reached in this study. Significant blood lymphocyte depletion was observed in all patients: median lymphocyte count at baseline was 46.6 (x 10^9/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. Response was evaluated at month 4 for the 11 evaluable patients, with an initial response rate of 64% (7/11) with a confirmed response at month 6 in 5/11 patients (45%) patients (all PRs). Four of the 11 patients 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 patients with B-cell lymphoma who relapsed or were refractory to a prior rituximab-containing regimen.

This trial utilized a 3+3 design, assessing dose levels of 450, 600, 900, and 1200 mg. No DLTs were observed amongst the 12 patients enrolled into the dose-escalation component, and expansion cohorts were subsequently undertaken at 600, 900, and 1200 mg. Induction therapy (doses of 450–1200 mg) consisted of 4 weekly infusions in cycle 1 for NHL and 3 weekly infusions in cycles 1 and 2 for CLL. Patients received ublituximab maintenance monthly during cycles 3–5, then once every 3 months for up to 2 years. Enrolled patients with B-NHL (n=27) and CLL (n=8) had a median of 3 prior therapies. No dose-limiting toxicities or unexpected adverse events (AEs) occurred. The most common AEs were infusion-related reactions (40%; grade 3/4, 0%); fatigue (37%; grade 3/4, 3%); pyrexia (29%; grade 3/4, 0%); and diarrhea (26%; grade 3/4, 0%). Common hematological AEs were neutropenia (14%; grade 3/4, 14%) and anemia (11%; grade 3/4, 6%). The overall response rate for evaluable patients (n = 31) was 45% (13% complete responses, 32% partial responses). Median duration of response and progression-free survival were 9.2 months and 7.7 months, respectively.[29]

b. Umbralisib

Umbralisib is a highly specific and orally available dual inhibitor of phosphoinositide-3-kinase (PI3K) delta (δ) and casein kinase 1 epsilon (CK1ε) with Nano molar 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.

Clinical Development of Umbralisib

Single-Agent in Patients with Relapsed or Refractory Hematologic Malignancies

Umbralisib has been evaluated in a single-agent Phase I dose-escalation study in patients with relapsed and refractory hematologic malignancies.[30] A total of 90 patients were enrolled and treated. The median age was 65 years (range 22-85) and 63% were male. Among all patients the median number of prior therapies was 3 (with a range of 2-5), with 44% refractory to prior rituximab-based chemotherapy. Histological diagnoses were as follows: FL (n=22), CLL (n=24), diffuse large B-cell lymphoma (DLBCL; n=16), Hodgkin's lymphoma (HL; n=11), mantle cell lymphoma (MCL; n=6), MZL (n=5), WM (n=3), hairy-cell leukemia (HCL) (n=1) and T-cell lymphoma (n=2). The majority of patients had an ECOG of 1 and 40/81 (49%) were refractory to prior therapy. Patients self-administered an umbralisib oral tablet once per day in 28-day cycles, with dose escalation done in a traditional 3+3 design to establish safety and determine the maximum tolerated dose. In initial cohorts, patients took umbralisib in a fasting state at a starting dose of 50 mg, increasing to 100, 200, 400, 800, 1200, and 1800 mg until the maximum tolerated dose was reached, or the maximal dose cohort was accrued without a dose-limiting toxicity. In an effort to further improve the oral bioavailability of umbralisib subsequent cohorts self-administered a micronized formulation of umbralisib tablet in a fed state at an initial dose of 200 mg, increased in increments to 400, 800, 1200, and 1800 mg until the maximum tolerated dose or the maximal dose level was accrued.

No maximum tolerated dose (MTD) reached. The most common treatment-emergent adverse events irrespective of causality were diarrhea (in 39 [43%] of 90 patients), nausea (38 [42%]), and fatigue (28 [31%]). The most common grade 3 or 4 adverse events were neutropenia (in 12 [13%] patients), anemia (eight [9%]) and thrombocytopenia (six [7%]). Serious adverse events considered at least possibly related to umbralisib occurred in seven patients: pneumonia in three (3%) patients, lung infection in one (1%), febrile neutropenia in one (1%), and colitis in two (2%), one of whom also had febrile neutropenia. The maximum tolerated dose was 1200 mg of the micronised formulation, with 800 mg of this formulation selected as the recommended phase 2 dose. Both cases of colitis occurred at above the recommended phase 2 dose. Thirty-three (37%) of the 90 patients enrolled had an objective response to treatment with umbralisib.

Umbralisib was clinically active in most patients treated. Fifty-six (62%) of the 90 enrolled patients had reductions in disease burden as assessed by CT scan, 33 (37%) had an objective response, and 30 (33%) had a partial response. No objective responses were recorded in the eight patients treated with less than 800 mg per day of the initial non-micronized formulation. Seventy-three patients were eligible for inclusion in the modified intention-to-treat population for assessment of antitumor activity. Of these 73 patients, 53 (73%) had reductions in disease burden, including 33 (45%) patients with an objective response of reductions of 50% or more of which three (4%) were a complete response and 30 (41%) were a partial response.

In patients with follicular lymphoma, nine (53%) of 17 patients achieved an objective response, including two (12%) who achieved a complete response; the remainder had a partial response.

Overall, umbralisib was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts with 800 mg QD (once a day) selected as the Phase 2 dose in patients with previously treated CLL and NHL. Umbralisib is now in Phase 3 development for patients with CLL (UNITY-CLL study). In conclusion, the safety, activity, and pharmacological properties of umbralisib support investigations of its use as monotherapy or in combination with other novel targeted drugs for patients with hematological malignancies.

c. Ublituximab in Combination with Umbralisib

The combination of ublituximab and umbralisib is currently under evaluation in registration trials in CLL and various B cell NHL histologies. Results of a Phase I/Ib study in subjects with relapsed or refractory NHL and CLL have been reported.[31] In early cohorts, patients received ublituximab on days 1, 8 and 15 of Cycles 1 & 2, then on day 1 of Cycles 4, 6, 9, and 12. In later cohorts, the ublituximab administration schedule was amended to infusions on days 1, 8, and 15 of Cycle 1, followed by Day 1 of Cycles 2 through 6. CLL patients receive Cycle 1, Day 1 infusions split over Days 1 and 2. Umbralisib was taken once daily until patients are removed from study as per the protocol.

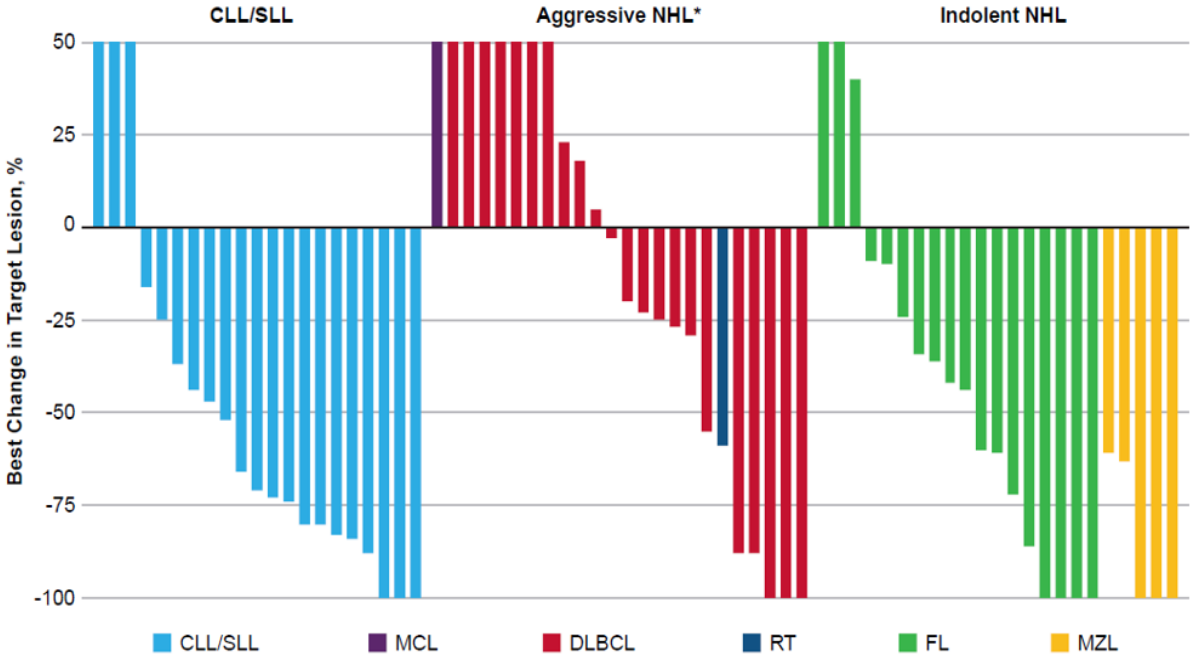
A 3+3 dose-escalation design is being utilized to evaluate sequentially higher doses of the combination agents as illustrated below:

Cohort	Ublituximab NHL Dose	Ublituximab CLL Dose	Umbralisib Dose (QD)
1	900 mg	600 mg	800 mg
2	900 mg	600 mg	1200 mg
3	900 mg	900 mg	400 mg (micronized)
4	900 mg	900 mg	600 mg (micronized)
5	900 mg	900 mg	800 mg (micronized)
6	900 mg	900 mg	1200 mg (micronized)

Enrollment completed in March 2017 with 75 subjects evaluable for safety and 69 subjects evaluable for efficacy. The MTD was not reached in the CLL (N = 22) or NHL cohort (N = 53). The median age of all subjects was 64 years (range 26 – 86). Subjects had a median of 3 prior therapies, and 57% were refractory to their immediate prior therapy.

Diarrhea was the most prevalent adverse event (60% all grades; 8% G ≥ 3), followed by nausea (56% all grades; 4% G ≥ 3), fatigue (48% all grades; 3% G ≥ 3), neutropenia (32% all grades; 28% G ≥ 3), vomiting (31% all grades; 1% G ≥ 3), and infusion related reactions (31% all grades; 1% G ≥ 3). The median time to onset and resolution of diarrhea was 21 days (range, 1 – 838 days) and 7 days (range, 1 – 191 days), respectively. Diarrhea was Grade 3/4 in 6 subjects. Management of Grade 3/4 diarrhea included dose hold (5 cases) and anti-diarrheal medication (3 cases), and all cases resolved. Biopsy-confirmed colitis was reported in 1 subject, and it was managed with treatment hold and steroids. Other Grade 3/4 events observed in greater than 5% of subjects included pneumonia (8%) and abdominal pain (7%). Grade 3/4 alanine transaminase (ALT) and aspartate transaminase (AST) elevations occurred in 3% and 1% of subjects, respectively. One subject with transaminitis received steroid treatment, and 1 case resolved without intervention. ALT/AST elevations of any grade had a median time to onset of 55 days. Pneumonitis was seen in 2 subjects with a median resolution time of 21 days (range, 15–28 days). Treatment was discontinued due to adverse events in 13% of subjects and 15% of subjects had their umbralisib dose reduced.

Efficacy data from all doses of the U2 regimen based on 68 out of 69 subjects evaluable for efficacy are presented in the waterfall plot below.



Response by histology in subjects receiving therapeutic dose levels and above of umbralisib (≥ 1200mg non-micronized or ≥ 600mg micronized) in combination with ublituximab is shown in the following table.

Histology	Response, n/N (%)				
	ORR	CR	PR	SD	PD
All patients	**29/57 (51)**	**12/57 (21)**	**17/57 (30)**	**11/57 (19)**	**17/57 (30)**
CLL/SLL	**10/15 (67)**	**2/15 (13)**	**8/15 (53)**	**2/15 (13)**	**3/15 (20)**
Aggressive B-NHL	**6/22 (27)**	**3/22 (14)**	**3/22 (14)**	**5/22 (23)**	**11/22 (50)**
DLBCL	5/19 (26)	3/19 (16)	2/19 (11)	5/19 (26)	9/19 (47)
MCL	0/2 (0)	–	–	–	2/2 (100)
RT	1/1 (100)	–	1/1 (100)	–	–
Indolent B-NHL	**13/20 (65)**	**7/20 (35)**	**6/20 (30)**	**4/20 (20)**	**3/20 (15)**
FL	8/15 (53)	4/15 (27)	4/15 (27)	4/15 (27)	3/15 (20)
MZL	5/5 (100)	3/5 (60)	2/5 (40)	–	–

Abbreviations: B-NHL, B cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SLL, small lymphocytic lymphoma.

Safety profile supports continued investigation of ublituximab and umbralisib in combination and in other multi-drug regimens: triple therapy combinations adding novel agents to ublituximab and umbralisib are ongoing (including with ibrutinib, bendamustine, and pembrolizumab) with additional triple therapy studies planned.

The combination of ublituximab and umbralisib is in registration directed trials in CLL (Study UTX-TGR-304 [UNITY-CLL]; NCT02612311), and various NHL subtypes, (Study UTX-TGR-205 [UNITY-NHL]; NCT02793583). See the latest Investigator's Brochure for updated information regarding the clinical development of ublituximab and umbralisib as single-agents or in combination.

1.2 RATIONALE

Despite improvements in the treatment of indolent lymphomas, the disease remains incurable. Thus, there is a continued need to improve treatment outcomes. The optimal treatment for newly diagnosed indolent lymphomas is based on tumor burden with options ranging from watchful waiting to single agent rituximab to chemoimmunotherapy regimens and most recently immunomodulator containing regimens.[12-15] Very few prospective trials have been conducted in the low tumor burden subgroup of indolent lymphomas. The only trial in the rituximab era was a trial by Ardeshna et al wherein it was found that rituximab improved progression free survival, however, the study did not show any improvement in overall survival.[24] Based on previously described efficacy outcomes of single agent rituximab there is clearly ample scope to increase response rates and overall outcomes after front line therapy. Toward achieving the goals of improving outcomes in low tumor burden indolent lymphomas, we propose to use single agent ublituximab as induction therapy. Given the toxicity seen with standard combination treatment regimens in patients, an initial chemotherapy free regimen with a potent CD20 antibody such as ublituximab followed by a response driven addition of a chemotherapy-free targeted agent may be an attractive treatment option if found to be well tolerated and to have significant anti-tumor activity.

Patients who achieve responses less than a CR are usually followed with an expectant strategy or are treated with extended duration rituximab. It is obvious that these patients are at a high risk of progression. To date, there has not been much data-driven guidance on how to manage these "at-risk" patients until frank progression occurs. Treating these patients with novel targeted inhibitors has the potential to halt expected progression and thus, preclude these patients from the receipt of more toxic therapies at disease progression. Multiple targeted inhibitors are currently being tested in patients with lymphoma. The phosphatidylinositol-3-kinase (PI3K) pathway has an important role in many cellular functions, including B-cell antigen receptor signaling. Selective inhibition of PI3K isoform δ-dependent signaling has direct antitumor activity and exerts pleiotropic effects in the tumor microenvironment of B-cell malignancies, inducing apoptosis and reducing proliferation.[32] Idelalisib, a first-in-class drug targeting the PI3Kδ pathway, was approved for use in 2014 in the USA and the European Union after showing clinical activity in patients with relapsed or refractory CLL and FL.[33] Similar to other B-cell receptor inhibitors, idelalisib is administered indefinitely until disease progression or intolerable toxicities occur. However, studies documented unexpected life-threatening adverse events with this drug, including an increased risk of autoimmune complications (e.g., colitis, pneumonitis, and transaminitis) and infections (e.g., cytomegalovirus reactivation and Pneumocystis jirovecii pneumonia). These adverse events have driven the need for not only efficacious, but also safer therapies.

Umbralisib, as shown in the multiple studies above, is associated with low rates of immune-mediated toxicity and exhibits a favorable long-term tolerability profile at a median follow-up of 1.3 years, with up to 5 years of overall follow up. The mechanism for decreased immune-mediated toxicity is still being elucidated through ongoing pre-clinical and correlative studies examining umbralisib's selectivity for PI3Kδ over PI3Kγ, complimentary CK1ε inhibition, and enhancement of regulatory T-cell function (Davids et al Abstract # PF444 EHA 2018).

In patients who do not achieve a CR, we propose to administer ublituximab plus umbralisib for a defined time duration (12 cycles) to assess if the addition of umbralisib can convert suboptimal responses to a CR. Ublituximab in combination with umbralisib is well tolerated and highly active in a broad population of heavily pretreated and high-risk patients with NHL and CLL.[32] Most studies so far have been designed with fixed duration ublituximab and umbralisib being administered until progression or unacceptable toxicity. The unique feature of our proposed hypothesis is fixed duration administration of umbralisib with the hope of enhancing efficacy as well as mitigating toxicity.

Pastore et al have shown that a clinicogenetic risk model (m-7FLIPI) includes the mutation status of seven genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300, FOXO1, CREBBP*, and *CARD11*), the FL International Prognostic Index (FLIPI), and the Eastern Cooperative Oncology Group (ECOG) performance status, improves risk stratification for failure-free survival (FFS) and overall survival in patients with FL receiving first-line immunochemotherapy.[10] The utility of this risk model is unknown in patients with FL who have been previously untreated or treated with chemotherapy-free approaches. The correlative analysis will include identifying m-7FLIPI risk model for each FL, which can help predict CR rates to single and combination therapy.

2 POTENTIAL RISKS AND BENEFITS

2.1 POTENTIAL RISKS

SINGLE AGENT UBLITUXIMAB

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

UBLITUXIMAB + UMBRALISIB COMBINATION

Adverse Events and Potential Risks

Refer to the most recent Investigator's Brochures IBs for ublituximab and umbralisib, which are updated periodically, for current safety information on the combination of ublituximab and umbralisib.

SINGLE AGENT UMBRALISIB

Adverse Events and Potential Risks

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

2.2 KNOWN POTENTIAL BENEFITS

Ublituximab has demonstrated evidence of clinical activity in relapsed NHL's including relapsed FL and MZL. Ublituximab may increase the likelihood of improved responses as compared to rituximab in indolent lymphomas. Furthermore, this trial also studies the combination of ublituximab and umbralisib in patients who do not achieve a CR to single agent therapy. The combination of ublituximab and umbralisib has shown to be safe and efficacious in relapsed indolent lymphomas. This trial provides an opportunity to test this combination in patients who have a suboptimal response to ublituximab with the hope of improving outcomes. The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: Potential to improve management and outcomes of malignancy
- To Society: Improved understanding of the role of Anti CD20 antibody and PI3K inhibitor in the management of indolent B cell NHL. Improved understanding of QOL assessments in indolent lymphomas
- Justify the importance of the knowledge gained: Anti-CD 20 antibody therapy and PI3K inhibitors have led to improved outcomes in patients with several subtypes of B-cell NHLs. However, there is a relative paucity of information regarding the efficacy of these agents as single agents or in combination in newly diagnosed indolent B-cell NHLs. This protocol will provide valuable insights into the potential role of these agents in the management of these lymphomas.

3 OBJECTIVES

Primary objectives:

To determine Best Complete response (CR) rates as measured by PET/CT scan at anytime during treatment with single agent or combination therapy

Secondary objectives:

- To determine overall response rates (ORR) in the entire cohort
- To assess safety and tolerability profile of single agent and combination therapy

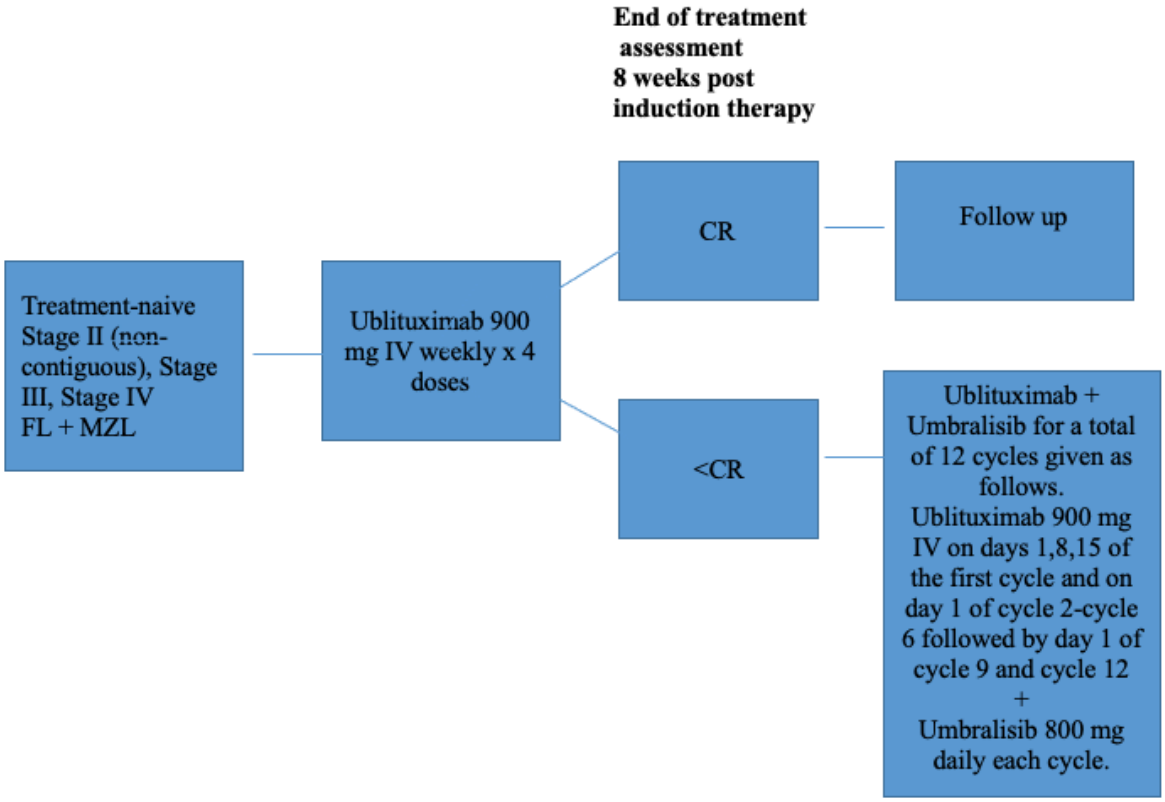
Exploratory objectives:

- To determine ORR and CR rates after induction therapy in FL and MZL cohorts
- To determine ORR and CR rates after combination therapy in the entire FL and MZL cohorts
- To determine Partial response (PR), Stable disease (SD), progressive disease (PD) rate of single agent and combination therapy
- To assess duration of remission of single agent and combination therapy
- To assess 2-yr progression free survival (PFS) and overall survival (OS) of single agent and combination therapy
- To explore baseline disease and patient factors that may predict response to ublituximab alone and with umbralisib
- To assess rates of transformation to aggressive lymphoma
- To evaluate the health-related quality of life (QoL) of subjects as assessed by the following subject-reported questionnaire:
    - FACT-Lym, a standardized instrument for use as a measure of health-related QoL as highlighted in the **APPENDIX** section
- Correlative analysis: M7FLIPI testing at diagnosis may be performed which can help predict CR rates with single versus combination therapy. Patient samples will be tested in a CAP/CLIA-accredited laboratory on a custom next generation sequencing (NGS) panel. This panel consists of 310 genes, which are recurrently mutated across clonal hematopoietic proliferations including clonal hematopoiesis of indeterminate potential (CHIP), acute and chronic myeloid neoplasms, B- and T-cell lymphomas, and plasma cell neoplasms. Specifically included in this panel are the full coding sequences of the seven genes in the m7-FLIPI clinicopathologic riskmodel: *ARID1A*, *CARD11*, *CREBBP*, *EP300*, *EZH2*, *FOXO1*, and *MEF2B*. (Pastore et al. Lancet Oncol 2015).[10] Mutation data will be analyzed by a board-certified molecular pathologist and these results will be incorporated with clinical data to determine the m7-FLIPI score.
- Minimal residual disease assessment may be performed on patient samples.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is an open-label, Phase II interventional study in order to assess the safety and efficacy of single agent ublituximab as initial therapy for FL and MZL with response driven addition of umbralisib for suboptimal response.



Based on overall reporting in low tumor burden FL and MZL, CR rate of at least 30% was achieved when single agent rituximab was used in these subsets. We assume that by administering ublituximab (both as a single agent and in combination for individuals who fail to achieve a CR with the single agent), the CR rate will increase to 50%. Efficacy will be assessed using the proportion of patients treated with ublituximab alone or with ublituximab administered in combination who have a complete response. Thus, we will test the efficacy of ublituximab using a difference in proportions design by comparing an expected study population control rate of 50% to the comparison proportion being determined by the historical control CR rate of 30%. In other words, the null hypothesis is that the true response rate is 30%, and it will be formally tested against a one-sided alternative that the response rate is 50%.

A total of 24 patients will need to be accrued (assuming 73% power and a type I error of 0.10 when the true response rate is 50%). At study completion, the proportion of patients achieving a complete response will be calculated, along with 95% confidence intervals for this proportion. Assuming 20% screen fail/drop-out rate, 30 patients need to be screened for this study.

Patients will be followed for outcome measures up to 2 years from study enrollment. Study enrollment will continue until stopping endpoints. Of note, the study will accrue continuously, and will not stop enrollment of patients while analysis of stopping endpoints are underway.

Toxicity

Treatment-related mortality: If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team. The study will be terminated prematurely if at any point 2 patients experience treatment-related death secondary to the study regimen (Ublituximab and/or umbralisib)

Toxicities of special interest:

a. Patients enrolled on the single agent treatment Ublituximab will be assessed for toxicities of special interest for 30 days. The study will be halted prematurely if more than 5 patients experience the following toxicities:

- Grade 4 Neutropenia
- Neutropenic Fever

b. The combination arm of Ublituximab + Umbralisib is of special interest in this study. Patients enrolled on this arm will be assessed for toxicities of special interest for 90 days. The study will be halted prematurely if more than 3 consecutive patients enrolled on the combination arm experience any of the following toxicities:

- Grade 3 or higher pneumonitis
- Grade 3 or higher colitis
- Grade 4 hepatitis
- Grade 4 rash
- Other grade 4 unmanageable events attributable to the study treatment.

c. The study will be halted prematurely if a patient develops progressive multifocal leukoencephalopathy on single agent / combination arm of the study.

Patients will continue to receive study therapy as defined by the schema (4 weekly doses of ublituximab in the single agent treatment and ublituximab plus daily umbralisib for a total of 12 cycles in the combination arm) or until disease progression according to Cheson 2014, unacceptable toxicity, death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), patient or physician decision to withdraw, or pregnancy, whichever occurs first. The study will end when all patients enrolled have completed planned treatment or the Sponsor decides to end the trial, whichever occurs first.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

Efficacy: Best Complete response (CR) rates at anytime during treatment with single agent or combination therapy as defined by the Lugano response Criteria for NHL (Cheson 2014)

4.2.2 SECONDARY ENDPOINTS

Efficacy: To determine Overall response rates (ORR) in the entire cohort as defined by the Lugano response Criteria for NHL (Cheson 2014)

Toxicity:
Ublituximab tolerability as per CTCAE V5.0 criteria
Umbralisib tolerability as per CTCAE V5.0 criteria

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

Screening for eligible subjects will be performed within 28 days before study entry unless stated otherwise in the Schedule of Events. Prior to study entry, each potential subject must satisfy all of the following inclusion criteria. Obtaining pathology samples is not required prior to enrollment, but confirmation of availability is required prior to enrollment.

Disease Related

1. Subjects with histologically documented Follicular lymphoma CD20+ (Grade 1, 2 or 3a) *OR* Marginal zone lymphoma CD20+ (nodal, extranodal or splenic) according to World Health Organization (WHO) criteria.
2. Ann Arbor Stage II (Non-contiguous), III or IV disease
3. Patients must have a whole body or limited whole body PET/CT scan performed within 42 days prior to registration. CT portion of PET/CT will be done with contrast based on current NCCN guidelines unless patient has borderline renal function or allergic to contrast dye.
4. Patients must have bone marrow biopsy performed within 6 months prior to registration
5. Measurable node must have an LDi greater than 1.5 cms. In the absence of nodal lesions, measurable extranodal disease should have an LDi greated than 1 cm. In patients with Splenic Marginal Zone lymphoma, in the absence of nodal lesions, spleen size should should be over 14 cms with evidence of lymphoma in the bone marrow biopsy.
6. For low tumor burden lymphomas (as determined by GELF criteria) [7]: Include patients diagnosed within 2 years of diagnosis. Low tumor burden patients diagnosed more than 2

years from study entry will be allowed provided patients have documented progression.

Prior Therapy Criteria

1. Patients must be untreated advanced stage disease (Stage III or Stage IV) or Stage II (non-contiguous). (Exception: Involved field or involved site radiation given for localized diagnosis is not considered a line of therapy).

Clinical/Laboratory Criteria

1. Patients must be ≥ 18 years of age and be able to swallow and retain oral medication
2. ECOG performance status of 0-2
3. Patients must have adequate bone marrow function as evidenced by ANC ≥ 1000/μL and platelets ≥ 50,000μL and Hb >= 8g/dl within 28 days prior to registration unsupported by growth factors.
4. Serum creatinine < 2.0 mg/dL or calculated creatinine clearance (CrCl) > 45 mL/min
5. Patients must have adequate hepatic function obtained within 28 days prior to registration and documented by all of the following:
    - Total bilirubin ≤ 1.5 x IULN (≤ 5 x IULN if secondary to lymphoma, Gilbert's syndrome, or medication related)
    - Direct bilirubin ≤ 1.5 x IULN (≤ 5 x IULN if secondary to lymphoma)
    - AST and ALT ≤ 2.5 x IULN (≤ 5 x IULN secondary to lymphoma)
6. Patients must be willing to receive *Pneumocystis jirovecii* prophylaxis with sulfamethoxazole/trimethoprim, dapsone, and atovaquone or inhaled pentamadine, if they initiate combination umbralisib plus ublituximab (not for single agent ublituximab)
7. Patients must have a complete history and physical examination within 28 days prior to registration
8. Patients with follicular lymphoma must have the following components of Follicular Lymphoma International Prognostic Index (FLIPI) available from diagnosis, and collected again at time of registration:
    - Age
    - LDH
    - Number of nodal groups involved
    - Serum or plasma hemoglobin
    - Ann Arbor Stage

    Additionally, patients must have beta$_2$-microglobulin collected at time of registration and response assessment.
9. Female subjects of reproductive potential must have a negative serum pregnancy test within 3 days prior to treatment start date. Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy at least six weeks ago) are exempt from pregnancy testing. 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.

10. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence, or sterilized partner) and a barrier method (e.g., condoms, cervical ring, sponge, etc.) during the period of therapy.

    The following are UNACCEPTABLE forms of contraception for females of childbearing potential:

    - natural family planning (rhythm method)
    - breastfeeding
    - fertility awareness
    - withdrawal

    For subjects, these birth control requirements must be adhered to for 4 months (120 days) after the last dose of umbralisib or ublituximab, whichever is later.

Regulatory Criteria

1. Patients ***must*** be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

5.2 EXCLUSION CRITERIA

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

Disease-Related

1. Transformed lymphoma; if clinical evidence of transformed lymphoma is present, transformation should be ruled out by biopsy of the suspicious lymph node/lesion
2. Prior treatment for follicular lymphoma or marginal zone lymphoma (Except: involved field or site radiation therapy is allowed)
3. Medically apparent central nervous system lymphoma or leptomeningeal disease
4. Tumor burden where administration of other FDA approved anti-CD20 antibodies like single-agent rituximab would be inappropriate.
5. Patients in need of immediate cytoreduction with chemotherapy based regimen.

Concurrent Conditions

1. Evidence of chronic active Hepatitis B (HBV, not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), active cytomegalovirus (CMV), or known history of HIV (or positive HIV test during screening). If HBc antibody is positive, the subject must be evaluated for the presence

of HBV DNA by PCR. If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. See Appendix: HEPATITIS B SEROLOGIC TEST RESULTS. If the subject is CMV IgG or CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. Subjects with positive HBc antibody and negative HBV DNA by PCR are eligible. Subjects with positive HCV antibody and negative HCV RNA by PCR are eligible (subjects who are CMV IgG or CMV IgM positive but who are CMV DNA negative by PCR are eligible).

2. For subjects with a prior known history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening, contraindication or intolerance to antiviral agents effective against hepatitis B.
3. Ongoing drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by stones, or cirrhosis of the liver
4. Inflammatory bowel disease (such as Crohn's disease or ulcerative colitis)
5. Irritable bowel syndrome with greater than 3 loose stools per day as a baseline
6. Active autoimmune disease requiring ongoing immunosuppressive therapy including systemic corticosteroids (prednisone or equivalent ≤10 mg daily allowed as clinically warranted) within 12 months prior to enrollment. Patients are allowed to use topical or inhaled corticosteroids or levothyroxine for hypothyroidism or hypogylcemic agents for diabetes mellitis.
7. Any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
   - Symptomatic, or history of documented congestive heart failure NYHA (New York Heart Association) functional classification III-IV [see Appendix: New York Heart Association Classifications]
   - Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, CHF, or myocardial infarction within 6 months of enrollment.
   - Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.
   - 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.
7. Women who are pregnant or lactating
8. Live virus vaccines within 4 weeks prior to ublituximab therapy, or planned administration of live virus vaccines during ublituximab therapy
9. History of other malignancies (including myelodysplastic syndromes) **except:**
   - malignancy treated with curative intent and with no known active disease present for >2 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician
   - adequately treated non-melanoma skin cancer without evidence of disease
   - adequately treated carcinoma in situ without evidence of disease

- 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 study entry

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Newly presenting patients with treatment-naive follicular lymphoma and marginal zone lymphoma at the University of Colorado Blood Disorders Center (UCD BDC) will be presented with the options of standard of care therapy versus study participation. The study will also be posted on clinicaltrials.gov. Given the benefit observed for ublituximab and umbralisib in multiple indolent subtypes, we anticipate that patients may be referred to UCD BDC specifically to enroll in this trial.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

If a patient chooses to voluntarily withdraw from study, then documentation must be made regarding if patient chooses to simply discontinue study treatment, or if patient also no longer wants to be followed for treatment outcomes (and thus opts out of study related follow-up).

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

- Patient experiences treatment related intolerable toxicities that persist despite following the guidelines for dose modifications and dose reductions, including supportive care measures. Treatment may be delayed to recover from toxicity for a maximum of eight weeks (56 days).
- Disease progression assessed by Lugano response Criteria for NHL (Cheson 2014)
- The subject may withdraw consent at any time for all or certain aspects of the study as follows:
    - Withdraw consent for study treatment, but allow Follow-up Period assessments and data collection on subsequent anti-lymphoma therapy and PFS
    - Withdraw consent for study treatment and Follow-up Period assessments, but allow data collection on subsequent anti-lymphoma therapy and OS
    - Withdraw all consent
- Inability of the patient to comply with study requirements
- Non-compliance/lost to follow-up
- Conditions requiring therapeutic intervention not permitted by the protocol
- Pregnancy
- Discontinuation of the study
- Investigator discretion

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Should a patient choose to withdraw voluntarily from the study at any time, study drug will be terminated, and the patient will proceed to be treated according to standard of care. Study-related information accumulated prior to the patient's withdrawal of consent will be analyzed according to intention to treat analysis.

After withdrawal from protocol treatment, patients should be followed for AEs for 30 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.

Subjects that discontinue study drug will remain on study and continue to follow specified follow-up procedures. If a subject wishes to withdraw consent for all study-related follow-up, then the patient should notify the investigator of this request. The patient's request should be in writing if possible. The investigator should document in the medical records in detail if the patient's withdrawal is from study treatment or also from all study-related follow up. However, an investigator may consult public records, such as those establishing survival status.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY (STUDY STOPPING RULES)

Teleconferences will be held with the study sponsor to exchange findings and unexpected results that may occur in patients participating in this study. The study will be terminated based on toxicity stopping rules as discussed in section 8.5. Any new information suggesting the study intervention may be harmful in study population will be shared with the COMIRB. The principal investigator will discuss any such new information via conference with TG Therapeutics, Inc., and if warranted, may choose to terminate study.

6 STUDY AGENTS

6.1 STUDY AGENT AND CONTROL DESCRIPTION

Guidelines for Administration of Ublituximab

- *Method of Administration:* Ublituximab will be administered as an intravenous infusion through a dedicated line. All infusions will be administered per institutional guidelines. During ublituximab monotherapy (initial treatment), Cycle 1 Day 1 administration time frame: Over 4 hours (+ 30 minutes). Cycle 1 days 8 and 15 will be over 3 hours (+ 30 minutes), and Cycle 1 Day 22 will be over 90 minutes (+ 20 minutes). During combination treatment with umbralisib, ublituximab will be administered over 90 minutes (+ 20 minutes).
- *Days of administration:* Ublituximab at dosage of 900mg will be administered on C1D1, D8, D15 and D22 of induction therapy (total 4 doses). During combination treatment

with umbralisib, ublituximab 900mg will be administered on Days 1, 8 and 15 during the first cycle of combination treatment, on Day 1 of Cycle 2 through Cycle 6, followed by Day 1 of Cycle 9 and Cycle 12

- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:* Pre-medications should include an antihistamine (diphenhydramine 50 mg or equivalent), and a **corticosteroid (dexamethasone 10-20 mg or equivalent).**
    - If pre-medications are given via IV route, the ublituximab infusion should begin approximately 30 minutes after the conclusion of the last pre-medication infusion If pre-medications are given via oral administration, the ublituximab infusion should begin 45-60 minutes after ingestion of the oral pre-medications.If a pre-medication is poorly tolerated, consider decreasing its dose, using a different drug or discontinuing, if clinically appropriate. Adjusting antihistamine and corticosteroid doses, adjusting the timing of administration and/or additional pre-medications may be used at investigator discretion for additional prophylaxis against infusion related reactions.
    - Use of oral acetaminophen 650 mg (or equivalent) may be used in patients who experience fever or pyrexia after week 1 dose, or as clinically warranted based on investigator discretion.
- *Patients with a prior known history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening:* Prophylaxis with an antiviral agent effective against hepatitis B is required. Consider consulting clinicians with an expertise in managing subjects with a prior history of hepatitis B regarding monitoring and consideration of options for hepatitis B antiviral therapy for prophylaxis/treatment. Monitor subjects closely as clinically indicated based on liver tests and any observed signs/symptoms such as jaundice, abdominal pain, dyspepsia, dark-colored urine often accompanied by lighter-than-normal colored stools, nausea, vomiting or fatigue.
- *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.
- *Patient 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 TG Therapeutics, Inc. at *productquality@tgtxinc.com* with any product quality concerns or questions.
    - No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).
    - Concurrent glucocorticoid therapy as long as started 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, **consider holding antihypertensive medications 12-24 hours prior to and throughout infusion of ublituximab. Decision to withhold antihypertensive medication is at investigator discretion.**

- For patients at risk for tumor lysis syndrome, in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

Ublituximab should not be mixed with other medicinal products. Ublituximab should only be diluted in 0.9% NaCl before use. No data are available for other solutions such as 5% dextrose and 5% mannitol.

Ublituximab is available in 150 mg (6 mL quantity vial) and 900 mg (36 mL quantity vial) single use vials as a 25 mg/mL concentrate for dilution. Dilutions for ublituximab are as follows:

Dose of ublituximab for infusion	Volume of ublituximab (25 mg/mL)	Volume of NaCl 0.9% to be removed	Final volume in perfusion bag
900 mg	36 mL	36 mL	500 mL

Infusion Rate Recommendations for Ublituximab Administration

Ublituximab monotherapy induction: Cycle 1 Day 1 infusion over 4 hours (+ 30 minutes)

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

Ublituximab monotherapy induction: Cycle 1 Day 8 & 15 infusions over 3 hours (+ 30minutes)

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

Ublituximab monotherapy induction: Cycle 1 Day 22 infusion over 90 minutes (+ 20 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

Ublituximab combination treatment with umbralisib: infusions over 90 minutes (+ 20 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

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 patients 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.

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

The following are recommended infusion rate reduction/delay guidelines for patients who experience severe Infusion Related Reactions (IRR's) that result in treatment interruption. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator.

1st or 2nd Infusion Interruption:

- Hold infusion and closely monitor patient, institute symptomatic medical management until resolution of IRR symptoms.
- Following the judgment of the Investigator, and provided the patient is stable, the infusion may be resumed at no more than half the previous rate.
- If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose (see Flow Rate Recommendations for Ublituximab Administration).

3rd Infusion Interruption (same day):

- Discontinue infusion for that day – monitor patient for resolution of all symptoms. Patient 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 patient from study site.
- Any remaining diluted investigational product should be discarded.

If an infusion is discontinued, the next scheduled dose should be administered according to the protocol dosing schedule.

Guidelines for Administration of Umbralisib

- *Dose of administration:* 800 mg PO daily
- *Method of Administration:* Umbralisib will be administered orally once daily within 30 minutes of starting a meal.
- *Potential Drug Interactions*: No drug interactions have been reported to date.

- *Pre-medications:* Patients receiving umbralisib are required to start prophylaxis treatment with *Pneumocystis jiroveci* pneumonia (PJP) and antiviral therapy prior to Day 1 of Cycle 1.
    - *Anti-viral Prophylaxis:* Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent.
    - *PJP Prophylaxis:* Dapsone 100 mg daily or Trimethoprim-Sulphamethoxazole twice a week. Other options include atovaquone or inhaled pentamadine.
- Final choice of PJP and anti-viral prophylactic therapy is per investigator discretion.
- 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 Investigator Discretion.

Umbralisib will be dispensed by the research pharmacy or designee at the site. Patients must be provided drug in its original container. Patients should be instructed to return all empty and partially filled bottles including any unused tablets when they return to the site. Study drug compliance should be reviewed with the patient using a patient drug diary at the beginning of each new treatment cycle and as needed.

Umbralisib should be taken at approximately the same time each day within 30 minutes of starting a meal. Patients should be instructed to swallow the tablets as a 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.

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. Immediately inform TG Therapeutics, Inc. at *productquality@tgtxinc.com* with any product quality concerns or questions. The pharmacist or his/her representative should record all umbralisib drug dispensations.

6.1.1 DOSING SCHEDULES

1) Patients with Stage II (non-contiguous), Stage III and Stage IV Follicular lymphoma and Marginal zone lymphoma will receive ublituximab 900 mg IV weekly for 4 doses (days 1, 8, 15 and 22)
2) At 8 weeks after completion of ublituximab monotherapy, patients will undergo PET-CT assessment.
3) Patients who do not achieve a CR after ublituximab monotherapy will receive a combination of ublituximab and umbralisib for a total of 12 cycles given as follows: ublituximab 900 mg IV on Days 1, 8 and 15 during the first cycle of combination treatment, on Day 1 of each subsequent 28-day cycle through Cycle 6 and then every 3 cycles (i.e. C9 and C12) PLUS umbralisib 800 mg PO daily on Days 1-28 of each 28-day cycle.

4) Patients with CR on either single or combination therapy will be followed with scans for 2 years.

6.1.2 DOSE ADJUSTMENTS FOR TOXICITY

Patients should be assessed clinically for toxicity at each visit using the NCI CTCAE v5.0 (*http://evs.nci.nih.gov/ftp1/CTCAE*) grading scale. Dosing should occur only if a patient's clinical assessment and laboratory test values are acceptable.

Dose Delay/Modifications: Ublituximab

- No reduction in the dose of ublituximab is permitted.
- Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities.
- Ublituximab should be discontinued if treatment is delayed for greater than 56 days due to toxicity.
- If the patient 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.
- For patients with a prior history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening who experience an increase in liver enzymes while on study, hold ublituximab immediately and assess for active hepatitis B infection.
    - If negative for hepatitis B, ublituximab may be resumed.
    - If reactivation of hepatitis B is confirmed, institute hepatitis B antiviral treatment. Ublituximab may be resumed at investigator discretion once hepatitis B infection has resolved, with continued monitoring as described above.

Table 2: 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. If delay is > 56 days, discontinue ublituximab.
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. If delay is > 56 days, discontinue ublituximab.
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 or if delay > 56 days, discontinue ublituximab.
*See guidance above under **Dose Delay/Modications: Ublituximab** for patients with a prior history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening who experience an increase in liver enzymes while on study	

Dose Delay/Modifications: Umbralisib

- Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities.
- Umbralisib should be discontinued if treatment is delayed for greater than 56 days due to toxicity.
- If the patient withdraws consent or has documented progression, an end of study visit should be completed.

Table 3: Umbralisib Dose Delay and/or Modifications Guidance

NCI-CTCAE Grade	Dose Delay and/or Modification
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 current dose. Consider supportive care. If recurrence after re-challenge, delay umbralisib until Grade ≤ 3 and/or neutropenic fever or infection is resolved; thereafter, resume umbralisib at current dose or 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.

NCI-CTCAE Grade	Dose Delay and/or Modification
Grade 4 thrombocytopenia	Delay umbralisib until Grade ≤ 3; thereafter, resume at current dose. Consider supportive care intervention as warranted. If delay is > 56 days, discontinue umbralisib. If recurrence after re-challenge, delay umbralisib until Grade ≤ 3; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator.
Pulmonary & Related Infections*	
Grade 1 or 2	Provide supportive care as warranted. Stop all therapy and hold until complete resolution. Restart umbralisib at one lower dose level. Restart ublituximab at full dose. If recurrence after re-challenge, discontinue umbralisib. If applicable, hold ublituximab. Upon resolution, resume ublituximab at full dose and schedule.
Grade ≥ 3	Provide supportive care as warranted. Discontinue umbralisib and ublituximab.
***For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at investigator's discretion. While pneumonitis has been minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-herpetic viral prophylaxis is required prior to the start of therapy.**	
Liver Injury (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Grade 1	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Monitor labs every 1-2 weeks. Maintain full dose and schedule of ublituximab, if applicable.***

NCI-CTCAE Grade	Dose Delay and/or Modification
Grade 2	Maintain current umbralisib dose level. Assess concomitant medications and risk factors*. **Begin supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent per investigator discretion) **.** Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off. Maintain full dose and schedule of ublituximab, if applicable.*** If liver toxicity recurs to Grade 2: o Re-initiate steroids. o Monitor labs at least weekly until Grade 1. o Consider delaying umbralisib. o If applicable, consider delaying ublituximab.*** o Once resolved to Grade ≤1 o If umbralisib was delayed, restart umbralisib at current dose. o If applicable: if ublituximab was delayed, restart ublituximab at full dose and schedule.*** o Taper prednisone by 10 mg per week until off.
Grade ≥ 3	Delay umbralisib. Assess concomitant medications and risk factors*. Begin/continue supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent per investigator discretion) **. Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1: o Restart umbralisib at one lower dose level. o Taper prednisone by 10 mg per week until off. If applicable, delay ublituximab until ≤ grade 1; thereafter, resume ublituximab at full dose and schedule.***
* 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. ***See guidance above under **Dose Delay/Modications: Ublituximab** for patients with a prior history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening who experience an increase in liver enzymes while on study.	
Diarrhea and/or Colitis	

NCI-CTCAE Grade	Dose Delay and/or Modification
Diarrhea Grade ≤ 2	Provide supportive care as warranted. If tolerable, maintain current dose of umbralisib. Otherwise, delay umbralisib until ≤ grade 1. Resume umbralisib at current dose level. If recurrence after rechallenge, delay umbralisib until ≤ grade 1; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator. **NOTE**: If persistent grade 2 diarrhea despite supportive care, delay umbralisib until ≤ grade 1; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator. If umbralisib is delayed for > 2 cycles at any time, discontinue umbralisib. If applicable, maintain full dose and schedule of ublituximab. If intolerable or persistent grade 2 diarrhea despite supportive care, delay ublituximab until ≤ grade 1; thereafter, resume ublituximab at full dose and schedule. If ublituximab is delayed for > 2 cycles at any time, discontinue ublituximab.
Diarrhea Grade ≥ 3	Provide supportive care as warranted. Delay umbralisib until Grade ≤ 2; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of investigator If recurrence after rechallenge, delay umbralisib until Grade ≤ 1; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator. If umbralisib is delayed for > 2 cycles at any time, discontinue umbralisib. If applicable, delay ublituximab until ≤ grade 2 (or until ≤ grade 1 for recurrence after rechallenge); thereafter, resume ublituximab at full dose and schedule. If ublituximab is delayed for > 2 cycles at any time, discontinue ublituximab.

NCI-CTCAE Grade	Dose Delay and/or Modification
Colitis (all Grades)	Provide supportive care as warranted. Delay umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level. If umbralisib is delayed for > 2 cycles at any time, discontinue umbralisib. If applicable, delay ublituximab until resolution; thereafter, resume ublituximab at full dose and schedule. If ublituximab is delayed for > 2 cycles at any time, discontinue ublituximab.
All Other Non-Hematological Adverse Events	
Grade ≤ 2	Maintain current dose level. Provide supportive care as warranted.
Grade ≥ 3	Provide supportive care as warranted. Delay umbralisib until Grade ≤ 2; thereafter, resume umbralisib at current dose. If recurrence after re-challenge, delay umbralisib until Grade ≤ 2; thereafter, resume umbralisib at current dose or next lower dose level at discretion of the investigator. If umbralisib is delayed for > 2 cycles at any time, discontinue umbralisib.

Umbralisib 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 patient requires a dose reduction of umbralisib due to study drug related toxicity, the dose may not be re-escalated. If further evaluation of the toxicity reveals the event was not related to umbralisib, this 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.

On the combination treatment, if ublituximab is discontinued due to toxicity, umbralisib should be continued through 12 cycles as planned. If umbralisib is discontinued due to toxicity, ublituximab may be continued at investigator discretion. Any questions related to discontinuation of treatment should be directed to the Principal Investigator, and

NCI-CTCAE Grade	Dose Delay and/or Modification
patients should not be discontinued from both ublituximab and umbralisib due to toxicity without discussion with the Principal Investigator.	

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES AND OVERVIEW

Ordering Ublituximab and Umbralisib

Ublituximab and TGR-1202 (umbralisib) are available from TG Therapeutics, Inc. Please allow 5 to 7 business days between drug ordering and drug arrival. Order ublituximab Monday through Wednesday to ensure shipment does not arrive on a weekend day. Ensure staff will be available to unpack shipment immediately upon arrival. Please direct drug orders to ISTdrugorder@tgtxinc.com. The email should include the following:

- Requested quantity of TG Therapeutics, Inc. study drug(s)
- Date needed
- Principal Investigator name
- Study title
- TG Therapeutics, Inc. tracking number (U2-NTG-009)
- Investigational drug pharmacy shipping address
- Total number of study subjects enrolled to date
- Number of study subjects currently receiving each TG Therapeutics agent

Upon receipt of this shipment, the clinical trial designee at our site will 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 designee will document it during the acknowledgement of receipt and contact TG Therapeutics, Inc. at productquality@tgtxinc.com.

The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed and doses/vials destroyed. The Drug Accountability Log will be reviewed during any site visits and at the completion of the study.

STUDY MEDICATION OVERVIEW

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) and 36 mL (900 mg) single-use glass vials.

Storage: Ublituximab vials must be stored in a secured, limited-access, refrigerated area at a temperature ranging from 2-8°C (36-46°F). Ublituximab must not be frozen. Temperature should be monitored, documenting minimum and maximum daily.

Stability: Once a vial of ublituximab has been diluted, it must be used immediately or be stored refrigerated. The storage duration of ublituximab diluted in polyvinyl chloride (PVC) or non-PVC polyolefin (PO) material is up to 24 hours when refrigerated at 2-8°C (36-46°F). After allowing the diluted bag to come to room temperature, use immediately.

Expiration memorandums will be provided noting lot expiration dates. For questions about expiry email *productquality@tgtxinc.com*.

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), or
- One vial containing 900 mg solution of ublituximab

The container closure system of ublituximab is a type I glass vial closed by a siliconized chlorobutyl rubber stopper and a tamperproof protective cap crimped to the neck of the vial

Availability: Ublituximab is available from TG Therapeutics, Inc.

Umbralisib (TGR-1202)

Classification: Dual inhibitor of Phosphatidylinositol-3-Kinase (PI3K) Delta and CK1 epsilon

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:	Umbralisib must be stored in a secured limited-access area between 20°C and 25°C. Excursions permitted between 15°C and 30°C. Do not freeze.
Stability:	Expiration memorandums will be provided noting lot expiration dates. For questions about product expiry email *productquality@tgtxinc.com*.
Route of Administration:	Oral
Packaging:	Umbralisib is provided in HDPE bottles each containing 30 tablets and a silica gel canister as a desiccant.
Availability:	Umbralisib is available from TG Therapeutics, Inc.

6.3 POST-STUDY ACCESS

At the end of the study period, TG therapeutics, Inc. will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study and TG Therapeutics, Inc. provides written approval. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgment of the Investigator to treat the condition under study.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES /EVALUATIONS

PET/CT: A scan is done at baseline as part of the initial staging evaluation. PET/CT scan performed within 42 days prior to registration. PET scans, in conjunction with diagnostic-quality CT scans, will be obtained in this study. PET-CT scans should include skull-base to mid-thigh. Full-body PET-CT scan should be performed when clinically appropriate.
CT scans with oral and IV contrast should include neck, chest, abdomen, and pelvic scans. In patients for whom contrast is contraindicated, (e.g., patients with contrast allergy or impaired renal clearance or patient denial), CT or combined PET-CT scans without contrast are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period.

For Follicular lymphoma patients: All response assessments will be PET/CT based.

For Marginal Zone lymphoma patiens: If Baseline PET/CT does NOT demonstrate uniformly

FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY. If Baseline PET/CT demonstrates uniformly FDG avid lesions subsequent assessments on the study will be done with PET/CT scans.

A PET/CT will be done 8 weeks post completion of induction therapy (EOI PET/CT) with single agent ublituximab.

Patients who achieve a CR (Lugano response Criteria for NHL (Cheson 2014) will be followed by PET/CT done at the 6 months, 12 months, 18 months and 24 months post EOI (end of induction treatment) PET/CT. After this, imaging will be performed at the discretion of the investigator.

Patients who do not achieve a CR will initiate therapy with combination umbralisib and ublituximab. On this combination treatment, a PET/CT will be done prior to Cycle 4, cycle 8 and Cycle 12. Patients who achieve a CR during these time points will continue on combination therapy for the entirety of the 12 cycles course of treatment.

A PET/CT will be done 12 weeks post completion of combination therapy (EOT PET/CT).

Patients on the combination treatment who are post completion of 12 cycles of therapy will enter the follow up period in which a PET/CT will be done at the 6 months, 12 months, 18 months and 24 months post EOT PET/CT.

Bone Marrow Biopsy: Patients with FL and MZL must have a bone marrow biopsy performed within 6 months prior to registration. For patients with FL, response assessment of bone marrow involvement by lymphoma will be by PET scan only and bone marrow aspirates and biopsies will not be required for assessment of disease response.. For patients with MZL a restaging bone marrow biopsy will be done 8 weeks post completion of induction therapy with single agent ublituximab if a staging bone marrow biopsy was previously positive. On the combination arm, a bone marrow biopsy (if initially involved) will be done 12 weeks post completion of 12 cycles of therapy if a staging bone marrow biopsy was previously positive.

Post-Trial Assessments: Patients who go off study treatment at any time during the trial will complete end of treatment assessments per section 7.3. For all patients, drug-related SAEs and AEs will be followed until baseline or ≤ grade 1 levels for a total of 30 days. Patients who responded or maintained stable disease during the study will be followed for date of disease progression. Patients may refuse to participate in the post-trial assessments.

Clinical Evaluations: Patients should be seen and evaluated by provider as follows:

Single agent induction therapy: Day 1, Day 8, Day 15, Day 22, 4 weeks and 8 weeks post completion of therapy.
Patients achieving CR to single agent therapy: Will be evaluated in clinic every 3 months for 2 years.
Patients not achieving a CR: Will start Combination therapy.

Combination therapy: Patients will be evaluated on Day 1, Day 8 and Day 15 of C1, and on Day 1 and Day 15 of C2; subsequently, they will be evaluated on Day 1 for cycles 3-12.
After completion of combination therapy, patients will be evaluated in clinic 4 weeks post completion of therapy, 12 weeks post completion of therapy, and then every 3 months for 2 years and every 6 months for years 2 through 5.

Patients should be seen and evaluated by physician no less than one time every 16 weeks (4 cycles).

7.1.1 RESPONSE ASSESSMENT

The timing of PET/CT and Bone marrow biopsy on each single agent and combination therapy arms of the trial have been outlined in 7.1.

Patients with a global deterioration of health status requiring permanent discontinuation of study treatment (taken off study) without objective evidence of disease progression and without evidence of other causes to attribute to deteriorating health will be counted as progressive disease. Every effort should be made to document the objective progression even after discontinuation of treatment. Deaths of unknown cause and those related to malignancy or treatment-related toxicity will be counted as treatment failure.

Patients will be analyzed with respect to imaging-based CR, overall survival (OS) and progression-free survival (PFS). Overall survival is defined as time from the first chemotherapy administered on trial until death from any cause. For subjects who are still alive at the time of the study analysis or who are lost to follow-up, survival will be censored at the last recorded date that the subject was known to be alive. Progression-free survival is defined as time from therapy until relapse, progression, or death from any cause. Response will be determined by the principal investigator or the co-principal investigators.

Definitions for clinical response for patients with lymphoma are from the Lugano response criteria (Cheson et al. 2014).[34] Response assessment will be performed by treating provider, and will be performed at the University of Colorado.

Definitions of Tumor Response and Progression
Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The screening measurement will be taken as a reference for determinations of response. The nadir measurement will be taken as a reference for PD; this measurement constitutes the smallest measurement recorded, including the screening measurement if this is the smallest measurement. For FDG-avid tumors, metabolic criteria for response by PET-CT will take precedence over anatomic criteria for response by contrast CT when assessing CR.

For patients staged with PET-CT, focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CTcharacteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (eg, hepatic nodules) may be included in the six representative, measured lesions. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites). In patients in whom a discordant histology or malignant transformation is suspected, a PET-CT may identify the optimal site to biopsy for confirmation.

Revised Criteria for Response Assessment: Lugano Classification (cont.)

Response	Site	PET-CT-Based Response	CT-Based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to <= 1.5 cm in LDi No extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow Normal by morphology; if indeterminate, IHC negative	Normal by morphology; if indeterminate, IHC negative
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extralymphatic sites	Score of 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	>= 50% decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5mm x 5 mm, but smaller than normal, use actual measurement for calculation

Revised Criteria for Response Assessment: Lugano Classification (cont.)

Response	Site	PET-CT-Based Response	CT-Based Response
Partial (cont.)	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >= 50% in length beyond normal.
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or Stable Disease		**No metabolic response**	**Stable disease**
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	> 50% decrease from baseline in SPD for up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
	Nonmeasured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable

Revised Criteria for Response Assessment: Lugano Classification (cont.)

Response	Site	PET-CT- Based Response	CT-Based Response
Progressive Disease		**Progressive metabolic disease**	**Progressive disease (requires at least 1 of the following)**
	Individual target nodes/nodal lesions Extranodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: • LDi> 1.5 cm AND • Increase by >= 50% from PPD nadir AND • An increase in LDi or SDi from nadir • 0.5 cm for lesions <= 2 cm • 1.0 cm for lesions > 2 cm
	Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
	Organ enlargement		In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma.
	Bone marrow	New or recurrent FDG-acid foci	New or recurrent involvement

5-PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography (scan); PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment).

[b] PET 5PS: 1, no uptake above background; 2, uptake <= mediastinum; 3, uptake > mediastinum but < liver; 4, uptake moderately liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

7.2 LABORATORY PROCEDURES/EVALUATIONS

Local laboratory assessments as specified on the schedule of events table will include the following:

- Hepatitis B virus (HBV) testing will include hepatitis B surface antigen (HBsAg), antibody to the hepatitis B surface antigen (anti-HBs), and antibody to the hepatitis B core antigen (anti-HBc). If a subject is anti-HBc or HBsAg positive, a quantitative polymerase chain reaction test to measure viral DNA load will be performed. Interpretation of this test is described in the **Appendix** section
- Testing for HCV (testing for antibody; if positive then quantitative polymerase chain reaction test to measure viral RNA load).
- HIV testing will be performed per institutional guidelines.
- Testing for CMV, If CMV IgG or IgM is reactive, the subject must be evaluated for the presence of CMV DNA (by PCR).
- Hematology: Complete Blood Count (CBC) with absolute differential, including hematocrit, hemoglobin, white blood cell count (WBC) with differential, and platelet count.
- Chemistry: Comprehensive Metabolic Panel including albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate transaminase (AST/SGOT), bilirubin (total and direct), calcium, chloride, creatinine, glucose, phosphorous, potassium, sodium, total protein, serum urea/blood urea nitrogen (BUN), LDH, Uric acid.
- Serum beta$_2$-microglobulin.
- Thyroid function tests will include thyroid stimulating hormone (TSH) and free thyroxine (fT4).
- Calculated creatinine clearance (CrCl) will be estimated using the Cockcroft-Gault formula: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]; for females, the formula is multiplied by 0.85 (Cockcroft, 1976).
- Coagulation tests will include prothrombin time, international normalized ratio (INR) and partial thromboplastin time (PTT or activated PTT).
- Urinalysis (a urine dipstick may be used) will include color, appearance, specific gravity, pH, glucose, ketones, blood, bilirubin, and protein. A microscopic examination will be performed if urinalysis result is abnormal.
  Pregnancy testing will be performed for females of child-bearing potential. A serum pregnancy test must be done ≤ 3 days of starting treatment with single agent ublituximab induction.

7.2.1 Clinical Laboratory Evaluations (Research Procedures) - *Pathology*

Baseline standard of care diagnostic pathology samples will be performed as clinically indicated. Pathological materials including H&E stain, all IHC slides, and any leftover FFPE tissue block along with the pathology report from initial diagnosis should be sent to be reviewed, and the diagnosis confirmed by the University of Colorado pathology department (retrospective diagnostic review – treatment may commence prior to the University of Colorado review).

Obtaining pathology samples is not required prior to enrollment, but confirmation of availability is required prior to enrollment.

Initial diagnostic materials should be submitted within 30 days of patient enrollment. A copy of the pathology report should be sent when the sample is shipped.

The diagnostic slides and any leftover material will be returned after review.

7.2.2 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Pathology

H&E stain and IHC slides and any leftover FFPE tissue block along with the pathology report from initial diagnosis should confirmed by the University of Colorado hematopathology department .

Specimens from the tissue block will be stored in the HCTU bank for MRD studies, next generation sequencing and m7FLIPI testing.

Research Blood Samples

Research blood samples will be banked, and MRD studies, next generation sequencing and m7FLIPI testing may be conducted.

Research samples will be collected and stored under the University of Colorado Hematology Lymphoid Malignancy Tissue Bank (LTB) protocol. Patients must be tissue bank consented prior to sample collection and samples will be collected by the tissue banking team.

Correlative Analysis Blood Samples

Peripheral blood will be collected at the following time points (see study schedule for specifics):

- Baseline – within 28 days prior to first day of first cycle of study treatment
- Peripheral blood will be collected every time a PET CT assessment visit is conducted.
- For Example:
    - On single treatment: At the EOI PET/CT visit
    - On the combination treatment: Prior to Cycle 4, 8 and 12 of therapy
    - On the combination treatment: At the EOT PET/CT visit
    - For both single and combination treatments: At 6 months, 12 months, 18 months and 24 months post completion of therapy – last dose of ublituximab (for single agent treatment) and umbralisib (for combination therapy)
    - At recurrence or progression

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Informed Consent must be obtained prior to beginning any assessments solely for the purpose of this study. Informed consent will be reviewed with patient in detail by the physician or designee, with the physician or designee addressing all questions and concerns of the patient. Informed consent will be signed by patient and authorized consenting personnel should the risks/benefits be deemed acceptable to patient.

Screening evaluations will be performed for all subjects to determine study eligibility after signing the informed consent form. These evaluations must be completed within 28 days prior to administration of the first dose (Cycle 1 Day 1 [C1D1]) unless noted otherwise below.

The following will be performed or assessed at screening as specified in section 7.4:

- Complete medical history will be documented by a qualified clinician at the time of the Screening Visit. The medical history will be general enough to document common comorbid conditions as well as specific enough to confirm any condition against the eligibility criteria, and will document whether the identified conditions are active or inactive at the time of enrollment. Disease history will include specific information regarding diagnosis and histology including grade.

- Physical examination including evaluation of lymph nodes, spleen and liver will be performed.

- Demographics will include date of birth, sex, race, and ethnicity.

- Adverse event assessment (baseline AEs).

- Concomitant medications reviewed and documented.

- ECOG performance status will be recorded.

- Vital signs will include blood pressure, pulse, respiratory rate and body temperature.

- Body weight and height (height at the screening only) will be measured.

- Body surface area (BSA) will be calculated using the subject's height and weight according to local pharmacy practice.

- Serum pregnancy testing (in WOCBP) </= 3 days of starting treatment

- Counseling about pregnancy precautions and the potential risks of fetal exposure will be given to females of child-bearing potential and to all males.

- Tumor tissue sample for confirmation of diagnosis and correlative research (submitted within 30 days after registration – confirmation of *availability* is required). Patients

whose tissue is not available may still be eligible to go on trial if they choose to have a SOC biopsy during the screening period.

- Hematology (as outlined in section 7.2)
- Chemistry (as outlined in section 7.2)
- Urinalysis (as outlined in section 7.2)
- TSH and free T4
- PT/INR and PTT
- Serum beta$_2$-microglobulin
- HIV, HBV, HCV, CMV screen (as outlined in section 7.2)
- Creatinine Clearance
- PET-CT will be performed within 42 days of C1D1 of treatment
- 12-lead single electrocardiogram (ECG) will be recorded.
- Bone marrow biopsy analysis will be performed for patients with FL and MZL within 6 months prior to study registration)
- Subject self-reported health related quality of life will be assessed at Screening using the FACT-Lym questionnaire
- Research blood tubes will be collected for correlative analysis as described in this protocol.

Inclusion/exclusion criteria will be reviewed in detail to ensure that the patient is a study candidate prior to enrollment and subsequent treatment. If it is not clear if patient qualifies for study, the principal investigator should be notified for review of patient candidacy.

7.3.2 INDUCTION TREATMENT WITH SINGLE AGENT UBLITUXIMAB

Cycle 1 D1, D8, D15 and D22

If screening assessments are performed within 48 hours of Cycle 1 Day 1, safety laboratory and physical examinations need not be repeated at Cycle 1 Day 1.

Upon starting treatment, patients will be seen and evaluated by treating provider on C1D1, D8, D15 and D22. All laboratory, safety, and physical examinations should be performed by a provider or nurse within 48 hours of the start of every dose.

The following evaluations will be performed at these visits:

- Physical examination with vital signs and weight
- Adverse event assessment
- Concomitant medications
- Hematology (as outlined in section 7.2)
- Chemistry (as outlined in section 7.2)
- Ublituximab administration

7.3.3 END OF TREATMENT VISIT FOR SINGLE AGENT THERAPY

The End of Induction visit will occur at 8 weeks after completion of 4 doses of Induction Ublituximab and will include the following assessments:

- History and physical examination with vital signs and weight
- Adverse event assessment
- Concomitant medications
- ECOG performance status will be recorded
- Hematology (as outlined in section 7.2)
- Chemistry (as outlined in section 7.2)
- Urinalysis (as outlined in section 7.2)
- Serum beta$_2$-microglobulin
- End of induction treatment PET-CT and tumor response assessment 8 weeks after completion of 4 doses of single agent ublituximab. (For marginal zone lymphoma patients, If Baseline PET/CT does not demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY)

- If PET positive after the completion of induction therapy, a biopsy of PET positive area may be done at MD discretion.

- Bone marrow biopsy (for MZL patients) (this will be arranged ± 7 days of this visit) will be done 8 weeks post completion of induction therapy with single agent ublituximab if a staging bone marrow biopsy was previously positive.

- Subject self-reported health related quality of life will be assessed after completion of induction therapy using the FACT-Lym questionnaire

- Survival status will be assessed and subsequent therapy will be assessed

- Research blood tubes may be collected for biomarker analysis as described in this protocol

7.3.4 COMBINATION UBLITUXIMAB AND UMBRALISIB

Patients undergoing combination ublituximab and umbralisib will receive 12 cycles of treatment as follows: ublituximab 900mg IV on Days 1, 8 and 15 during the first cycle, on Day 1 of each subsequent 28-day cycle through Cycle 6, and then every 3 cycles (i.e. C9 and C12) and umbralisib 800mg daily. Patients will be seen by a provider or nurse within 7 days of every infusion (a physician must evaluate the patient at least every third cycle, i.e. no less than every 12 weeks during combination phase), and the following assessments will be performed:

- History and physical examination with vital signs and weight on D1 of all Cycles 1-12

- Adverse event assessment on D1 of all Cycles 1-12

- Concomitant medications on D1 of all Cycles 1-12

- Additionally, physical exam, vital signs and weight, hematology (as outlined in section 7.2), chemistry (as outlined in section 7.2), adverse event assessment and concomitant medications on D8 and D15 of C1, and physical exam, vital signs and weight, adverse event assessment and concomitant medications on D15 of C2

- ECOG performance status will be recorded on D1 of all Cycles 1-12

- Hematology (as outlined in section 7.2) on D1 of all Cycles 1-12

- Chemistry (as outlined in section 7.2) on D1 of all Cycles 1-12

- CMV surveillance by PCR every 3 cycles

- Serum $beta_2$-microglobulin on D1 of all Cycles 1-12

- Patients will be monitored for signs/symptoms of thyroid disorders, colitis, pneumonitis, hepatitis rash/dermatologic toxicity, changes in neurologic function. Patients will be monitored for infusion reactions.

    - Monitor subjects with a prior history of hepatitis B closely as clinically indicated based on liver tests and any observed signs/symptoms such as jaundice, abdominal pain, dyspepsia, dark-colored urine often accompanied by lighter-than-normal colored stools, nausea, vomiting or fatigue.

- PET-CT and tumor response assessment prior to C4, C8 and C12 of combination therapy
- (For marginal zone lymphoma patients, If Baseline PET/CT does not demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY)

- Subject self-reported health related quality of life will be assessed prior to C4, C8 and C12 of combination therapy using the FACT-Lym questionnaire

- Research blood tubes may be collected for biomarker/correlative analysis as described in the protocol prior to C4, C8 and C12 of combination therapy

7.3.5 END OF TREATMENT ASSESSMENT FOR COMBINATION THERAPY

The End of Treatment visit will be completed for subjects who are **withdrawn** from treatment for any reason as soon as possible (preferably within 3 weeks post last dose of treatment) after the decision to permanently discontinue treatment has been made. If a patient decision to withdraw from treatment occurs at a specific time point in the protocol, then that time point would be considered the EOT visit. For patients who come off treatment while on combination therapy prior to completing 12 cycles, the end of treatment visit will be as soon as possible. For patients on combination therapy who complete 12 cycles, the end of treatment visit will be on D+3 months (± 14 days) post last dose of treatment.

The following evaluations will be performed at the EOT visits:

- History and physical examination with vital signs and weight

- Adverse event assessment

- Concomitant medications

- ECOG performance status

- Hematology (as outlined in section 7.2)

- Chemistry (as outlined in section 7.2)

- Urinalysis (as outlined in section 7.2)
- Serum beta$_2$-microglobulin

End of treatment PET-CT and tumor response assessment (D+3 months (± 14 days)) post last dose of treatment. (For marginal zone lymphoma patients, If Baseline PET/CT does not demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY)

- Subject self-reported health related quality of life will be after completion of combination therapy using the FACT-Lym questionnaire
- Bone marrow biopsy (for MZL patients only if screening marrow was involved) (this will be arranged ±7 days of this visit)
- Survival status and subsequent therapy will be assessed
- Research blood tubes may be collected for biomarker analysis as described in this protocol

7.3.7 FOLLOW-UP

The follow-up period begins upon all study treatment discontinuation or completion as per protocol. This includes subjects who complete the full course of treatment and who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new anti-lymphoma therapy.

All subjects will be followed by provider for AEs and concomitant medications/procedures for 30 days after the last dose of ublituximab (for single agent treatment) and for 30 days after the latest of last dose of ublituximab or the last dose of umbralisib (for combination therapy).

The following evaluations will be performed at the follow-up visits:

- History and physical exam including vital signs and weight
- Laboratory evaluation (Hematology and Chemistry)
- AEs and concomitant medications will be evaluated

Patients will be seen in follow up every 3 months for the first 2 years post completion of therapy (last dose of ublituximab (for single agent treatment) and umbralisib (for combination therapy). PET/CT scans will be performed at the 6 months, 12 months, 18 months and 24 months post completion of therapy (last dose of ublituximab for single agent treatment) and umbralisib (for combination therapy). (If Baseline PET/CT for marginal zone lymphoma patients does not

demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY) At this time, patients will be seen by a provider for follow up of PD, subsequent anti-lymphoma therapy, or death. If at any point a patient decides to withdraw from long-term follow-up, there must be documentation of this decision by the provider, nurse or coordinator.

Subject self-reported health related quality of life using FACT-Lym questionnaire will be assessed at the 6 months, 12 months, 18 months and 24 months post completion of therapy (last dose of ublituximab (for single agent treatment) and the latest of last dose of ublituximab or the last dose of umbralisib (for combination therapy).

Research blood tubes may be collected at the 6 months, 12 months, 18 months and 24 months post completion of therapy (last dose of ublituximab (for single agent treatment) and the latest of last dose of ublituximab or the last dose of umbralisib (for combination therapy) for correlative analaysis as described in this protocol

7.3.8 EARLY TERMINATION VISIT

Early termination visits will be performed with the same requirements as the end of treatment visit (see section 7.3.6). (Imaging studies may be withheld if the last scan was done within 21 days of visit).

Note: if a patient chooses to voluntarily withdraw from study, then documentation must be made regarding if patient chooses to simply discontinue study treatment, or if patient also no longer wants to be followed for treatment outcomes (and thus opts out of study related follow up).

7.3.9 UNSCHEDULED VISIT/RECURRENCE OR PROGRESSION AT ANY UNSCHEDULED VISIT

The following evaluations will be performed if possible at all unscheduled visits:

- History and physical exam including vital signs and weight
- Laboratory evaluation and imaging as clinically indicated
- AEs and concomitant medications will be evaluated

The following evaluations will be performed at visits indicative of recurrence:

- History and physical exam including vital signs and weight
- Laboratory evaluation and imaging as clinically indicated
- Imaging study and biopsy if deemed fit by the clinical investigator

- Research samples may be drawn at this time for correlative analysis as described in this protocol

7.4- SCHEDULE OF EVENTS TABLE

Trial Period	**Screening**	**C1 (Single Agent Induction)[29]**					**End of Induction**	**Combination Treatment (Patients with < CR)**						**EOT[16 &18]**	**Follow-up (On Single Agent OR Combination Treatment)**		
								C1[15]		**C2**		**C3-12**		12 Weeks Post Completion of Combination Tx			
Treatment Cycle/Title	-28 to D0	D1[9]	D8	D15	D22	4 weeks post Induction Tx	8 Weeks Post Induction Tx	D1	D8 and D15	D1	D15	D1	D+4 weeks post combination Tx		3 M	6, 9, 12, 15, 18, 21 & 24 M	30 M+ Q6M Yrs. 2-5
Scheduling Window			± 1D			+7 days	± 7D	± 2D					+7 days	± 14D	± 28D		
Written Informed Consent	X																
Medical History	X						X	X		X		X					
Demographics	X																
Physical Exam	X	X	X	X	X	X[28]	X	X	X	X	X	X	X[28]	X	X	X	x
Vitals and weight[20]	X	X	X	X	X	X[28]	X	X	X	X		X	X[28]	X	X	X	x
Height	X																
ECOG Status	X						X	X		X		X		X			
ECG[7]	X																
PET with diagnostic quality CT Assessment[10]	X[5]						X[14]					X[19]		X[17]		X[21]	x[21]
Bone Marrow Biopsy	X[6]						X[11]							X[11]			
Adverse Event Assessment	X	X	X	X	X	X[28]	X	X	X	X	X	X	X[28]	X[20]	X	X	x
Concomitant Medications	X	X	X	X	X	X[28]	X	X	X	X	X	X	X[28]	X[20]	X	X	x
Survival Status & Subsequent Therapy							X							X	X	X	x
Ublituximab - 900 Mg IV		X[12]	X[12]	X[12]	X[12]			X	X	X		X[30]					
Umbralisib - 800mg PO Daily								X									
Hematology[13]	X	X	X	X	X	X[28]	X	X	X	X		X	X[28]	X	X	X	x
Chemistry[1]	X	X	X	X	X	X[28]	X	X	X	X		X	X[28]	X	X	X	x
TSH and fT4	X																
Creatinine Clearance	X																
Coagulation - PT/INR and PTT[4]	X																

Trial Period	**Screening**	**C1 (Single Agent Induction)[29]**					**End of Induction**	**Combination Treatment (Patients with < CR)**						**EOT[16 &18]**	**Follow-up (On Single Agent OR Combination Treatment)**		
								C1[15]		**C2**		**C3-12**		12 Weeks Post Completion of Combination Tx			
Treatment Cycle/Title	-28 to D0	D1[9]	D8	D15	D22	4 weeks post Induction Tx	8 Weeks Post Induction Tx	D1	D8 and D15	D1	D15	D1	D+4 weeks post combination Tx		3 M	6, 9, 12, 15, 18, 21 & 24 M	30 M+ Q6M Yrs. 2-5
Scheduling Window			± 1D			+7 days	± 7D	± 2D					+7 days	± 14D	± 28D		
Urinalysis[24]	X						X							X			
HIV Testing[23]	X																
Hep B[22]	X																
Hep C[23]	X																
CMV[23]	X							X[23]				X[23]					
Serum beta2-microglobulin	X						X	X		X		X		X			
Pregnancy Test[2]	X																
Research Blood Samples[8]	X						X					X[25]		X		X[26]	
Pathology Review[3]	X																
QOL Questionnaire (FACT-Lym)	X						X					X[27]		X		X[27]	

1. Chemistry will include uric acid, phosphorus, LDH and direct bilirubin. See section 7.2 for full list or required labs to be collected.
2. A serum pregnancy test for females of childbearing potential must be done ≤ 3 days of treatment start date with single agent ublituximab induction.. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.
3. Central review of pathology is required for confirmation of diagnosis. Completion of central pathology review is not required prior to registration for patients; however, confirmation of availability is required prior to enrollment and materials for central review must be submitted within 30 days after registration. Pathology material: H&E stain and IHC slides or a representative FFPE tissue block from initial diagnosis, including additional material for correlative analysis. Please NOTE: the diagnostic H&E slide and IHC slides will be returned after review. In addition, patients whose tissue is not available may still be eligible to go on trial if they choose to have an SOC biopsy prior to treatment.
4. PT/INR assessment frequency (for patients on Coumadin) is per investigator discretion to keep within therapeutic range.
5. Imaging must be done ≤ 42 days prior to study registration.
6. Screening bone marrow biopsy must be performed ≤6 months prior to study registration.
7. 12-lead single electrocardiogram (ECG) will be recorded.
8. Research blood samples (may be collected at screening and at all time-points when a PET CT is performed (i.e EOInduction, Prior to C4,8,12 of combination therapy, EOT, 6,12,18 and 24 months and at recurrence/progression) for correlative analysis as described in this protocol. Research samples will be collected and stored under the LTB protocol. Patients must be tissue bank consented prior to sample collection and samples will be collected by the tissue banking team.
9. If screening assessment are performed within 48 hours of C1D1, safety laboratory and physical examinations need not be repeated at Cycle 1.
10. Measurements can be done off the CT images of a PET/CT. (If Baseline PET/CT for marginal zone lymphoma patients does not demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY

11. Repeat bone marrow only required for MZL patients to confirm CR if initial bone marrow was positive. This will be arranged +/- 7 days of this visit. On the combination arm, a bone marrow biopsy (if initially involved for MZL) will be done 3 months post completion of 12 cycles of therapy.
12. During the induction treatment, patients will dose according to Dosing Schedule.
13. Hematology blood draws can be done before administration (not more than 2 days apart)
14. EOI PET CT will be performed within 8 weeks (+/- 7 days) post completion of single agent induction therapy. If PET positive after the completion of single agent induction therapy, a biopsy of PET positive area may be done at MD discretion. (If Baseline PET/CT for marginal zone lymphoma patients does not demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY)
15. The first cycle of Combination therapy will start (+ 2 week) after End of Induction imaging scan for patients not in CR. Patients on combination therapy will be seen at D1, D8 and D15 for C1, and D1 and D15 for C2 and then seen every 4 weeks for the remaining duration of therapy .
16. An end of treatment visit will be completed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made – this includes patients who continue on Combination therapy and come off treatment prior to completion of 12 cycles. For patients who continue combination therapy and complete 12 cycles, the end of treatment visit will be 12 weeks (+/-2 weeks) post last dose of umbralisib.
17. EOT PET CT will be performed within 12 weeks (+/- 7 days) post completion of combination therapy. (If Baseline PET/CT for marginal zone lymphoma patients does not demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY)
18. All subjects will be followed for AEs and concomitant medications/procedures for 30 days after the last dose of ublituximab (for single agent treatment) and umbralisib (for combination therapy). In addition, patients will be seen at 6 months, 12 months, 18 months and 24 months post completion of therapy (last dose of ublituximab (for single agent treatment) and umbralisib (for combination therapy) with PET/CT scans. At this time, they will be seen by a provider for follow up of PD, subsequent anti-lymphoma therapy or death. If at any point a patient decides to withdraw from long-term follow-up, there must be documentation of this decision by the provider, nurse or coordinator.
19. On the combination arm, a PET/CT will be done after prior to Cycle 4, cycle 8 and Cycle 12 (If Baseline PET/CT for marginal zone lymphoma patients does not demonstrate uniformly FDG avid lesions subsequent assessments on the study will be done with CT scans of the neck, chest,abdomen and pelvic scan with contrast ONLY)
20. Vital signs include blood pressure, pulse, respiratory rate and temperature.
21. Patients who achieve a CR will be followed by PET/CT done at the 6 months, 12 months, 18 months and 24 months post EOI PET/CT. After this PET/CT will be performed at the discretion of investigator judgement. Patients on the combination arm who are post completion of 12 cycles of therapy will enter follow up period in which case a PET CT will be done at the 6 months, 12 months, 18 months and 24 months post EOT PET/CT. After 24 months on either arms PET/CT can be performed based on investigator discretion.
22. Hepatitis B virus (HBV) testing will include hepatitis B surface antigen (HBsAg), antibody to the hepatitis B surface antigen (anti-HBs), and antibody to the hepatitis B core antigen (anti-HBc). If a subject is anti-HBc or HBsAg positive, a quantitative polymerase chain reaction test to measure viral DNA load.
23. Testing for HCV (testing for antibody; if positive then quantitative polymerase chain reaction test to measure viral RNA load), CMV testing by PCR every 3 cycles during treatment. HIV testing will be performed per institutional guidelines.
24. A microscopic examination will be performed if urinalysis result is abnormal.
25. Research samples to be collection prior to C4,C8 and C12 on combination therapy for correlative analysis as described in this protocol
26. 6 months, 12 months, 18 months and 24 months post completion of therapy – last dose of ublituximab (for single agent treatment) and umbralisib (for combination therapy)
27. Subject self-reported health related quality of life (FACT-LYM) will be assessed at screening and at all time-points when a PET CT is performed (i.e EOInduction, Prior to C4,8,12 of combination therapy, EOT, 6,12,18 and 24 months)
28. 4 weeks after last dose of Single agent Induction and Combination therapy patients will be seen in clinic for history and physical exam including vital signs and weight, lab evaluation including CBC and chemisty and AEs and concomitant medications.
29. All laboratory, safety, and physical examinations should be performed by a provider or nurse within 48 hours of the start of every dose.
30. Ublituximab will be administered every cycle (28 days) through Cycle 6, and then every 3 cycles (i.e. at Cycle 9 and Cycle 12).

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications reported in the CRF are concomitant prescription medications..

In addition, examples of acceptable methods of contraception include the following (also listed in section 5.1):

- Bilateral tube ligation
- Male sterilization
- Hormonal contraceptives that inhibit ovulation
- Hormone-releasing intrauterine devices
- Copper intrauterine devices

NOTE: Periodic abstinence (e.g. calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are **NOT** acceptable methods of contraception.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

- Antiemetics may be used at the discretion of the attending physician.
- Tumor lysis syndrome prophylaxis will be used at the discretion of the treating physician.
- Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. Growth factors should not be used to meet eligibility criteria. Pegfilgrastim support may be given during therapy. Treat as needed.
- Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.
- All blood products and concomitant medications such as anti-diarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose of study treatment will be recorded in the medical records.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The following medications are **prohibited** while on study treatment (exceptions noted):

- Treatment with immuno-suppressive **medications (except as used to treat drug-related adverse events)** will not be permitted unless discussed with and approved by the study principal investigator. This will be documented in the EMR system.
- Patients will also not be allowed to be treated with any concurrent anti-neoplastic therapy, including chemotherapy, non-palliative radiotherapy, and Chinese medications used for cancer treatment.

Treatment needs to be administered in collaboration with an oncology-trained pharmacist. Drugs that interact with ublituximab and umbralisib should be used with caution or avoided as per institutional guidelines.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

- Prophylactic medications, treatments and procedures should be performed according to institutional guidelines. This includes prophylactic antibiotics, anti-fungals, or PJP prophylaxis.
- Topical, inhaled, articular, intra-nasal corticosteroids are permitted. A brief (<3 weeks) course of steroids is permitted for purposes of prophylaxis (e.g. contrast) or treatment of non-auto-immune conditions (e.g. anaphylaxis).
- Patients receiving umbralisib are required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PJP) and antiviral therapy prior to Day 1 of Cycle 1 of combination treatment.
    - Anti-viral Prophylaxis: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent.
    - PJP Prophylaxis: Dapsone 100 mg daily. Other acceptable options include trimethoprim-sulphamethoxazole twice a week, atovaquone, or inhaled pentamadine.
- Final choice of PJP and anti-viral prophylactic therapy is per investigator discretion.
- 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 Investigator Discretion.
- Prophylaxis with an antiviral agent effective against hepatitis B is required in subjects with a prior known history of hepatitis B and for those with a positive antiHBc with negative HBsAg at screening.
- Promptly consult clinicians with an expertise in managing subjects with a prior history of hepatitis B regarding monitoring and consideration of options for hepatitis B antiviral therapy for prophylaxis/treatment.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Patients with adverse events while on study drug should be treated as indicated in section 6 of protocol. Other medical conditions that arise while patients are on study should be treated according to standard of care. The principal investigator should be made aware of serious adverse events occurring while patients are on study. Inquiries regarding handling of adverse events occurring while on study that are not described in this protocol should be directed towards the principal investigator.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

At the end of the study period, TG Therapeutics, Inc. will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study and TG Therapeutics, Inc. provides written approval. The investigator is responsible to ensure that the

subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A **non-serious adverse event** is an AE not classified as serious.

Laboratory Test Abnormalities:

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to TG Therapeutics, Inc. as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy

Overdose:

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations:

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following are <u>NOT</u> considered serious adverse events:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

This study will use the COMIRB definition of UAP. An unanticipated problem is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Grade 1: Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Grade 2: Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3: Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
- **Grade 4: Life-threatening**
- **Grade 5: Death**

8.2.2 RELATIONSHIP TO STUDY AGENT

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

8.2.3 EXPECTED ADVERSE EVENTS

Expectedness will only be documented for SAEs. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. All AE outcomes will be recorded as resolved or resolved without sequelae.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained (for SAEs) *or* from initiation of study treatment (AEs) until 30 days after the last day of study treatment. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

ADVERSE EVENTS

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

Adverse events will be documented in clinic notes at all scheduled visits. Adverse events will be graded by investigator according to CTCAE v5.0.

NON-SERIOUS ADVERSE EVENTS

Non-serious Adverse Events (AE) are to be provided to TG Therapeutics, Inc. in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement. The collection of non-serious AE information should begin at initiation of the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment. All non-serious adverse events can be assessed by telephone communication.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and new cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported).

SAE Reporting to TG Therapeutics, Inc.

SAEs require expeditious handling and reporting to TG Therapeutics, Inc. in order to comply with regulatory requirements. All SAEs (regardless of causality assessment) occurring from the time of consent through 30 days post last study treatment should be immediately reported to TG Therapeutics, Inc. at *safety@tgtxinc.com* (copy gabriel.green-lemons@tgtxinc.com and donna.gesumaria@tgtxinc.com) within 24 hours of the first knowledge of the event by the treating physician or research personnel on an SAE Form (MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable). **Include the TG Therapeutics, Inc.**

tracking number, U2-NTG-009 on the SAE report to TG Therapeutics, Inc., and indicate whether or not the SAE was designated a SUSAR.

SAE Reporting to the FDA and IRB

Investigator is responsible for reporting relevant SAEs to the FDA. Investigator is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the FDA within 7 calendar days after being notified of the event. Investigator will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs (SUSAR) associated with the use of the study medications to the FDA by a written safety report within 15 calendar days of notification. 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).

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

Study Drug Overdose

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

Overdose: An overdose as evaluated by investigator is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

In addition, all SAEs MUST also be sent to the following:

- The PI at *manali.kamdar@cuanschutz.edu*
- The OCRST at *CPDM.IIT@cuanschutz.edu*
- The DSMC at *DSMC@ucdenver.edu*

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the COMIRB criteria for UAPs require the creation and completion of a UAP report form. It is the site PI's responsibility to report UAPs to their IRB, using the IRB's standard UAP form. The Lead PI is responsible for reporting the UAP to the UCCC DSMC, if applicable. If an IRB UAP form is not provided, the UAP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

To satisfy the requirement for prompt reporting, UAPs will be reported using the following timeline:

- UAPs that are SAEs will be reported to the IRB and to the DSMC within 5 calendar days of the investigator becoming aware of the event.
- Any other UAP will be reported to the IRB and to the DSMC within 5 calendar days of the investigator becoming aware of the problem.

8.4.4 REPORTING OF PREGNANCY

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

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

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

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from study treatment, and the investigator must submit a Pregnancy Report Form to TG Therapeutics, Inc. within 24 hours of the first knowledge of the event by the treating physician or research personnel following the same process described for SAEs. Abortions (spontaneous, accidental, or therapeutic) must also be reported to TG Therapeutics, Inc. within 24 hours of awareness using the Pregnancy Report Form following the same process described for SAEs.

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, including reporting to TG Therapeutics, Inc.

In the event a subject's partner becomes pregnant, a Pregnancy Report Form should be completed and submitted to TG Therapeutics, Inc. within 24 hours of the first knowledge of the event by the

treating physician or research personnel following the same process described for SAEs, and the partner will be requested to consent to access to medical records. After the subject's partner provides consent, the pregnant partner and baby will be followed to see what effect the drug(s) under study may have on the outcome of the pregnancy or the health of the newborn. Additionally, medical information must be collected on the newborn for 6 months after birth, as permitted by local regulations.

Please see APPENDIX: CONTRACEPTION GUIDELINES AND PREGNANCY for additional information pertaining to following the pregnant female (and infant, if applicable).

8.5 STUDY HALTING RULES

Efficacy

Due to the small sample size, there will be no study halting rules based on efficacy.

Toxicity

If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team.

Treatment-related mortality: If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team. The study will be terminated prematurely if at any point 2 patients experience treatment-related death secondary to the study regimen (Ublituximab and/or umbralisib)

Toxicities of special interest:

a. Patients on the single agent treatment Ublituximab will be assessed for toxicities of special interest for 30 days. The study will be halted prematurely if more than 5 patients experience the following toxicities:

- Grade 4 Neutropenia
- Neutropenic Fever

b. The combination arm of Ublituximab + Umbralisib is of special interest in this study. Patients enrolled on this arm will be assessed for toxicities of special interest for 90 days. The study will be halted prematurely if more than 3 consecutive patients enrolled on the combination arm experience the following toxicities:

- Grade 3 or higher pneumonitis
- Grade 3 or higher colitis
- Grade 4 hepatitis

- Grade 4 rash
- Other grade 4 unmanageable events attributable to the study treatment.

c. The study will be halted prematurely if a patient develops progressive multifocal leukoencephalopathy on single agent / combination arm of the study.

Patients will continue to receive study therapy as defined by the schema (4 weekly doses of ublituximab in the single agent treatment and ublituximab plus daily umbralisib for a total of 12 cycles in the combination arm) or until disease progression according to Lugano response Criteria for NHL (Cheson 2014), unacceptable toxicity, death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), patient or physician decision to withdraw, or pregnancy, whichever occurs first. The study will end when all patients enrolled have completed planned treatment or the Sponsor decides to end the trial, whichever occurs first

8.6 SAFETY OVERSIGHT

Monitoring and Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial.

A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will

include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of the progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

Quality Control and Quality Assurance

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents.

Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

Based on overall reporting in low tumor burden FL and MZL, CR rate of at least 30% was achieved when single agent rituximab was used in these subsets.

We assume that Best CR Rates, i.e, CR rates at anytime during therapy—during single agent antibody therapy OR during combination therapy—will increase to 50% as compared to this 30% historical control CR rate. Sample size is determined using inference to a known proportion. Under a null hypothesis of 30% CR rate and an alternative hypothesis of 50%, then given a Type I

error rate of 0.10, a one-sided test, and a sample size of 24, then we have 73% power to detect a difference in complete response rate. Efficacy will be assessed using the proportion of patients who have a complete response. The null hypothesis that the true response rate is 30% will be tested against a one-sided alternative. 95% confidence intervals for the true complete response rate will also be calculated

Twenty-four patients are required for this single-stage design. Assuming 20% screen fail/drop-out rate, 30 patients need to be screened for this study.

10.2 STATISTICAL HYPOTHESES

Primary Endpoints

Efficacy: Best Complete response (CR) rates at anytime during treatment with single agent or combination therapy as defined by the Lugano response Criteria for NHL (Cheson 2014)

Efficacy will be measured by the proportion of patients who achieve a complete response to ublituximab alone or ublituximab plus umbralisib combination. Under current treatment protocols, if less than 30% of patients experience a complete response, then the treatment is considered a failure. Thus, for the experimental treatment, we define failure as an observed complete response rate less than 30%, and we define the null hypothesis as follows: H_0: $p_0 \leq 0.30$. Under the assumption that treatment with single agent or combination therapy will result in an observed complete response rate of at least 50%, we define the following alternative hypothesis: H_1: $p_1 \geq 0.50$. Complete response rate and associated 95% confidence intervals will be computed for the study.

Secondary Endpoints

Efficacy:
Overall response rates (ORR) (ie CR+ PR) in the entire cohort as defined by the Lugano response Criteria for NHL (Cheson 2014)

Rate of overall response in the entire cohort will be calculated, and a 95% confidence interval for ORR in the cohort will be calculated.

Toxicity:
Ublituximab tolerability as per CTCAE V5.0 criteria
Umbrasilib tolerability as per CTCAE V5.0 criteria

Regimen toxicities, as defined by CTCAE V5.0 will be summarized using tables and descriptive statistics. For each drug, the proportion of individuals experiencing toxicity events will be calculated, and 95% confidience intervals for these toxicity proportions will also be calculated. No formal hypothesis tests will be conducted with toxicity rates

10.3 ANALYSIS DATASETS

The primary efficacy analyses will be performed on the Intent-to-treat (ITT) population, which will include all subjects who have been enrolled for the study.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

The proportion of patients achieving a complete response (and associated 95% confidence intervals for this proportion) will be calculated for the patients being treated in this study. Three different complete response rates and associated 95% confidence intervals will be computed:
1—complete response rate to ublituximab alone
2—complete response to combination therapy
3—complete response to any therapy administered (i.e. complete response rate guided by the algorithmic approach set forth in this protocol)

The proportion of patients experiencing a drug-related SAE or grade 4-5 non-hematologic toxicity will be calculated for the patients being treated in this study along with 95% confidence intervals around this proportion.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The proportion of patients achieving a complete response will be calculated for the patients being treated in this study. This proportion will be formally compared to a null proportion of 30%. The population proportion and associated 95% confidence intervals will be calculated at study completion.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Secondary endpoints will be descriptive in nature, and no formal statistical analyses will be conducted on them.

The proportion of patients achieving an overall response and an accompanying 95% confidence interval will be calculated for the patients being treated in this study.

The proportion of patients experiencing a drug-related SAE or grade 4-5 non-hematologic toxicity will be calculated for the patients being treated in this study, and 95% confidence intervals around this proportion will also be reported.
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10.4.4 SAFETY ANALYSES

Regimen toxicities, as defined by CTCAE V5.0 will be summarized using tables and descriptive statistics.

10.4.5 ADHERENCE AND RETENTION ANALYSES

The PI will provide a DSM report to the UCCC DSMC on a six-month basis. The DSM report will include summaries of minutes taken at meetings (if applicable), the participants' demographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues (including a summary of any protocol deviations).

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Demographic data will be compiled for participants in the study at baseline, including age, gender, ethnicity, disease status, and comorbid conditions.

10.4.7 PLANNED INTERIM ANALYSES

No interim analyses are planned for this study.

10.4.8 SAFETY REVIEW

10.4.8.1 TOXICITY REVIEW

Response and toxicity data from the 24 treated patients will be assessed and the number of responses achieved will be tabulated.

10.4.8.2 EFFICACY REVIEW

After all 24 patients have been treated, efficacy will be assessed by complete response rate—regardless of treatment with ublituximab alone or in combination. Complete response rate to the treatment algorithm (as well as 95% confidence intervals around this complete response) will be calculated. In addition, complete response to ublituximab alone will be calculated (along with 95% confidence intervals), and complete response and 95% confidence intervals will also be computed for combination therapy alone.

10.4.9 ADDITIONAL SUB-GROUP ANALYSES

Though sample size is small, we plan to investigate complete response rates (and associated 95% confidence intervals) in the FL and MZL cohorts. Confidence intervals will likely be wide given that these cohorts will be subgroups of the original 24 patients.

10.4.10 EXPLORATORY ANALYSES

Secondary endpoints may lead to exploratory analyses outlined in 10.4.3.

Overall response rate, CR rate, PR rate, PD rate, and SD rate will be summarized for both the FL and MZL cohorts upon study completion.

Progression free survival (PFS) is defined as time from enrollment to PD or death of any cause. Patients who pass away without PD will be counted as if PD occurred on date of death. Patients without PD and did not pass away but are lost to follow up will have their information censored at date of most recent tumor assessment.

Overall survival is defined as time from enrollment to death due to any cause.

Median measures for 2-yr PFS and OS as well as remission duration will be assessed by conducting survival analysis. Kaplan-Meier survival methods will be used to estimate the survival function of these time-to-event outcomes.

Baseline disease and patient factors will be summarized.

Rates of transformation to aggressive lymphoma will be calculated.

Any assessment of minimum residual disease or assessment of next-generation sequencing will be analyzed.

QOL analysis will be performed: The change in Quality of life (QoL) scores as measured by FACT-Lym at the start of therapy and at the end of study will be assessed using a paired t-test and a null hypothesis of no change in QoL over the course of the study. Assessment of EuroQOL questionnaire has been shown in the **Appendix** section.

10.5 SAMPLE SIZE

The study will enroll 24-30 patients.

10.6 MEASURES TO MINIMIZE BIAS

In this non-blinded phase II study outcomes will be assessed by the principal investigator.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

To ensure the privacy and confidentiality of data for this protocol, the data will be stored on a restricted access server. Access to the project directory containing the data will be limited to the investigators and research staff. Information about data security awareness is promoted through user training and education and supplemented by policies and procedures. Password protection will

be used for all transactions that involve viewing, editing, and analyzing the data or that provide access to data fields derived from the original source documents.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by TG Therapeutics, Inc. and by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

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

consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate.

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

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

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

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the

study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating PIs, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor and by TG Therapeutics, Inc.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Intended Use:
Samples and data collected under this protocol may be used to assess biomarkers associated with response to therapy, for m7FLIPI testing, MRD analysis and for next generation sequencing.

Storage:
Access to stored samples will be limited to research personnel only. Samples and data will be stored using codes assigned by the investigators/designee. Data will be kept in password-protected computers. Only investigators/designees will have access to the samples and data.

Disposition at completion of the study:
Consent will be obtained from all patients for tumor tissue banking. Patients can withdraw consent for tumor banking at any time. All stored samples will be sent to the University of Colorado Hematology Lymphoid Malignancy Tissue Bank (LTB). Study subjects who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at the University of Colorado Cancer Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the, under the supervision of the primary investigator of the Hematology Lymphoid Malignancy Tissue Bank (LTB).

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the Hematology Lymphoid Malignancy Tissue Bank with the same goal as the sharing of data with the Hematology Lymphoid Malignancy Tissue Bank. These samples could be used for research into the causes of NHL its complications and other conditions for which individuals with NHL are at increased risk, and to improve treatment. The Hematology Lymphoid Malignancy Tissue Bank will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, and individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/ or samples will be provided to research personnel with permission from the Principal Investigator or desginee through the Hematology Lymphoid Malignancy Tissue Bank.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of

the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timelines of the data reported.

Source Documentation:

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained.

eCRF reported data will be submitted to TG Therapeutics, Inc. as requested.

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research.

An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

Electronic Case Report Forms (eCRF):

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into an electronic data capture system provided by the University of Colorado.

eCRFs are to be completed through use of a Sponsor-Investigator designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will

be entered directly from the source documents. All eCRFs should be completed by designated, trained site staff.

At the end of the study, any hard copy of patient data received by the investigator for his or her site must be stored safely with the study records. Acknowledgement of receipt of the compact disc is required.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official electronic study record.

Data Quality Assurance:

The Sponsor-Investigator will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Site will be responsible for data entry into the EDC system.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor-Investigator and records retention for the study data will be consistent with the Sponsor-Investigator's standard procedures.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations, or institution policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. Deviations will be reported to the DMSC and IRB according to UCCC DSM plan and institutional policy.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007 requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA (Food and Drug Administration Amendments Act) mandates that a "responsible party" (i.e., the sponsor or designated PI) register and report results of certain "applicable clinical trials".

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

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

16 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

17 LITERATURE REFERENCES

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Interpretation of Hepatitis B Serologic Test Results

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

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

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

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

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

www.cdc.gov/hepatitis

QoL Instrument – FACT-Lym Questionnaire

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

APPENDIX: 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.

APPENDIX: CONTRACEPTION GUIDELINES AND PREGNANCY

Females Not of Childbearing Potential are Defined as Follows:

Females 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 Females of Child-Bearing Potential:

Females of child-bearing potential, defined as all females physiologically capable of becoming pregnant, must use effective contraception during the study and for 120 days after the last dose of study treatment. Effective contraception is defined as either:

- True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- 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.
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomised male partner should be the sole partner for that patient.
- Oral contraception, injected or implanted hormonal methods.
- 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 females of childbearing potential:

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

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

Fertile Males

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment and for 120 days after the last dose of study treatment. They should also not father a child during this period.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to TG Therapeutics, Inc. within 24 hours of learning of its occurrence as outlined in the Safety Reporting section of this protocol. The pregnancy, both pregnant female and infant (if applicable), should be followed up for 6 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 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.

Principal Investigator:	**Manali Kamdar, MD, MBBS**
Phone:	**720-848-0752**
COMIRB No:	**18-2128**
Version Date:	**05/17/2021**
Study Title:	**Ublituximab as initial therapy for treatment-naive follicular or marginal zone lymphoma with response-driven addition of umbralisib for suboptimal response**

Key Information

Please read all the information below and ask questions about anything you don't understand before deciding if you want to take part.

You are being asked to be in a research study. Participation in Research is voluntary.

Purpose of the Study: We are doing this study to learn more about drugs to treat two types of Non-Hodgkin lymphoma (NHL). The two chemotherapy-free drugs are called Ublituximab and Umbralisib (the study drugs). The study drugs are not FDA approved to treat cancer and are considered to be investigational.

Procedures: If you agree to participate, the following will happen:

- You will have a screening visit to see if you are eligible for the study. This may include a bone marrow biopsy, PET/CT scan, and/or a tumor biopsy.
- If you are eligible and agree to participate, you will enter single phase induction, receiving Ublituximab through an intravenous infusion over several visits. You will have a bone marrow biopsy at the end of this treatment phase.
- If the single phase induction doesn't eliminate visible disease, Combination therapy will begin. Ublituximab will be administered intravenously on several days during the first cycle of combination treatment, and on Day 1 of each subsequent cycle through Cycle 6 and then every 3 cycles (i.e. Cycle 9 and Cycle 12) through Cycle 12. Umbralisib will be administered orally once a day. You will have a bone marrow biopsy at the end of this treatment phase.
- After combination therapy ends, the study doctor may continue you on single

phase or combination treatment for a varying length of time. You will be followed for two years after treatment ends.

- If you agree to participate, you will also be asked to participate in optional parts of this study.

- You may continue receiving study drugs for up to 12 cycles (approximately 6 months), and be followed every 3 months for the next 2 years.

Risks: Participation in research involves risks, including the following:

- **Risks associated with Ublituximab include:** changes in your blood count; fever; infusion related reaction; headache; digestive problems; fatigue and weakness; swelling of hands and/or feet; pain; liver disease, shingles; changes in taste; high blood pressure; throat problems; allergic reaction, itchy, red, and peeling rash that can be fatal; skin cancer; metabolic disorder; Hepatitis B reactivation; serious brain infection that can lead to death.

- **Risks associated with the Ublituximab+Umbralisib Combination include**: changes in your blood count; digestive problems; fatigue; infusion related reaction; decreased appetite; heart problems; ear problems; eye problem; chills; swelling; inflammation through the entire body; lung inflammation, infection, fluid build-up; liver problems; dehydration; failure to thrive; bone weakness; dizziness; change in taste; headache; anxiety; kidney problems; scrotal cyst; hair loss; high blood pressure; allergic reaction; itchy, red and peeling rash that can be fatal; skin cancer; serious metabolic disorder; serious brain infection that can lead to severe disability and death.

- **Risks associated with bone marrow biopsy include**: allergic reaction, pain, infection.

Benefits: There is no guarantee that your health will improve if you join this study. This study may lead to information that could help patients and health care providers in the future.

Alternatives: Please discuss standard treatment and care options with your doctor.

Detailed Consent

You are being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called **informed consent. If you decide to participate in this study, you will be asked to sign this form.**

Why is this study being done?

The purpose of this study is to learn more about drugs to treat two types of Non-Hodgkin lymphoma (NHL). The two chemotherapy-free drugs are called ublituximab and umbralisib. Ublituximab will be used to treat the tumor first, if the tumor does not respond well a second drug called umbralisib, will be added. You are being asked to be in this research study because you have been diagnosed with a type of NHL, follicular lymphoma (FL) or marginal zone lymphoma (MZL).

Neither drug is FDA approved for any type of cancer. These drugs and this drug combination are therefore considered to be experimental.

Throughout the rest of this consent form, ublituximab and umbralisib will be called the “study drugs”.

How many people will participate?

Up to 30 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

There are either 3 or 4 parts to the study (step 3 is skipped when disease is eliminated by step 2):

1. Screening (before beginning the study drugs)
2. Single Phase Induction (attempt to eliminate visible disease in your body)
3. Combination therapy (used if single agent treatment doesn’t eliminate visible disease)
4. Follow-up

By enrolling in this study you are forgoing standard of care therapy that has potential to decrease the amount of disease in your body.

The next section of this form lists what will be expected of you if you join this study.

Study Procedures

The screening tests and procedures will be done to see if you are eligible to join this study. You may have had some of these tests and procedures done recently as standard care for your cancer, and they may not need to be repeated.

- **Informed Consent**
  This informed consent form will be discussed with you and you will be given a copy of this document. If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures.

- **Medical and Cancer History**
  Before you start the study we will record your date of birth, race, ethnicity, and complete medical history. This history will look at the background and progress of your cancer and any treatments you have received for your disease.

- **Physical Examination**
  A physical examination will be completed as part of your standard of care. We will also assess if the study drug is affecting your body functions including lungs, heart, abdomen, extremities, skin, head (eyes, ears, nose, hair, etc.) and neurologically.

- **Vital Signs**
  We will take your blood pressure, heart rate, respiratory rate, body temperature and weight. Height will be measured only during screening.

- **ECOG Performance Status**
  We will assess how well you are performing your daily activities.

- **Review of Current Medications**
  Your study doctor will let you know which medications you can and cannot take while taking part in this study. From the time you first receive the study drugs through 30 days after the last dose, we will record medications you may be taking.

- **Review of Side Effects**
  Some risks have been identified because of the disease process or through use of the study drugs themselves and these will be followed very closely by the Principal Investigator and study staff. More information will be provided in the Risks section of this consent.

- **Routine Blood and Urine Samples**
  These tests are sometimes called safety labs so the study doctor can be sure it is safe for you to take part in this study and to be given the study drugs.
    - Pregnancy test: Women who are able to become pregnant will be given either a urine or a blood pregnancy test. A positive pregnancy test prior to being given the study drugs will exclude you from starting or continuing to take part in the study. This test must be performed within 3 days prior to starting treatment.
    - Complete blood count (CBC)
    - Comprehensive metabolic panel (CMP)
    - Blood clotting tests (PT/INR, and PTT)
    - Thyroid function tests (TSH)
    - Creatinine Clearance
    - Testing for HIV (human immunodeficiency virus)*, HBV (hepatitis B virus), HCV (hepatitis C virus), and EBV (Epstein-Barr virus)
    - Immune Function (CMV)
    - Tumor Assessment (B2MG)
    - Urinalysis

  *Positive HIV test result reported to the Colorado Department of Public Health and Environment as required by state law

- **Research Blood Samples for Banking (Optional)**
  These tests are being done specifically because you are participating in this study. These tests will be done to understand better how the drug is working. We will ask later in this form if you agree to allow these samples to be banked for future use.

- **Questionnaire on quality of life**
  These questionnaires will ask about you, your health, and how the treatment affects your day-to-day life.

- **Electrocardiogram (ECG or EKG)**
  This is a simple, noninvasive procedure that records the electrical activity of the heart. Electrodes are placed on the skin of the chest and connected in a specific order to a machine. Output usually appears on a long scroll of paper that displays a printed graph.
- **Bone Marrow Biopsy/Aspirate**

At various time points during the study, you will have bone marrow examined. This involves placing a hollow needle into your hip bone near the small of your back and taking a small sample of the bone (bone marrow biopsy) and 2-3 tablespoons of the liquid bone marrow inside the bone (bone marrow aspirate).

If a screening bone marrow biopsy is required, it needs to be done within 6 weeks prior to study enrollment. A repeat bone marrow biopsy prior to Cycle 3 would only be required to assess response if initial biopsy was positive for disease.

- **Imaging (CT)**
  These tests will be performed to check the status of your disease. These tests must be performed 4 weeks prior to study enrollment.
  - CT: A computed tomography scan uses x-rays to make detailed pictures of parts of the body and the structures inside the body.

- **Positron Emission Tomography (PET/CT) Scan**
  Positron emission tomography (PET) scan is a test that uses radioactive glucose (sugar) and a computer to create images of how organs and tissues in the body are functioning. Abnormal cells in the body use glucose at a different rate than normal cells and this allows the scanner to create a detailed picture of how your body is working. A PET/CT scan will be done before and after treatment. A CT scan may be performed in place of a PET/CT scan at other time points during the study, depending on your insurance carrier.

- **Tumor Tissue Samples**

  Archived Tissue: If you had surgery for your cancer in the past, we will need to request a portion of your tumor tissue from the institution where you had your surgery and that they have stored so we may use it for this to confirm your diagnosis of FL or MZL. Also, if you agree, we would like to store your tissue for future research.

  Tumor tissue biopsy during screening: If archived tissue is not available, we will ask you to allow us to take a fresh biopsy of your tumor tissue prior to treatment to confirm your diagnosis. This biopsy may be core needle, excisional, or incisional since fine needle aspirations are typically inadequate to make a diagnosis of FL or MZL. We will also ask you for permission to store it for optional future research.

- **Receiving the Study Drugs**

Ublituximab monotherapy: You will receive Ublituximab through an intravenous infusion, using a central venous catheter. This involves the insertion of a catheter, or small tube, into a large vein in the arm, or into a vein under your collar bone. This may be done under local anesthesia. Thirty-60 minutes prior to the Ublituximab infusion, you will receive an antihistamine and a corticosteroid. You will receive Ublituximab over a 4 hour infusion on day 1, a 3 hour infusion (days 8 and 15) and a 90 minute infusion on day 22.

Ublituximab combination therapy: Ublituximab will be administered intravenously on days on Days 1, 8 and 15 during the first cycle of combination treatment, and on Day 1 of each subsequent cycle through Cycle 6, and then every 3 cycles (i.e. Cycle 9 and Cycle 12) through Cycle 12.

Umbralisib: Umbralisib will be administered orally once daily within 30 minutes of starting a meal and should be taken at approximately the same time each day. Premedication treatments to prevent an allergic reaction will be given prior to day one of cycle 1.

Study Visits
Please refer to Study Calendar for schedule of events. In addition, please note the following information.

Screening
If screening tests and procedures are performed within 48 hours of Cycle 1 Day 1, routine lab testing and physical exams do not need to be repeated.

Induction Cycles
All screening tests and procedures must be done prior to treatment (up to 28 days prior to treatment, with the exception of PET/CT which can be done up to 42 days prior to treatment) and may be performed from up to 1 day prior to treatment.

If after your treatment with Ublituximab during the Induction cycles, the PET/CT scan shows evidence of disease, combined therapy of Ublituximab and Umbrasilib will be administered. The PET/CT scan should be within 8 weeks of cycle 1 day 1.

End of Treatment

For patients with no detectable disease as measured by PET/CT 8 weeks after induction with Ublituximab treatment ends.

For patients receiving combination therapy of Ublituximab and

Umbralisib, the end of therapy is reached 12 weeks after completion (last dose) of combination treatment.

Follow-Up

The follow-up period starts after the end of treatment visits. Patients will be seen in follow up every 3 months for the first 2 years post completion of therapy (last dose of ublituximab (for single agent treatment) and umbralisib (for combination therapy).

PET/CT scans will be performed at the 6 months, 12 months, 18 months and 24 months post completion of therapy (last dose of ublituximab for single agent treatment) and umbralisib (for combination therapy). At this time, patients will be seen by a provider for follow up of any progressive disease, subsequent anti-lymphoma therapy, or death.

Trial Period	Screening	C1 Single Agent					End of Induction	Combination						EOT	Follow-up (On Single Agent OR Combination Treatment)		
								C1		C2		C3-12[a]		12 Weeks Post Completion of Combination Tx			
Treatment Cycle/Title	-28 to D0	D1	D8	D15	D22	4 weeks post Induction Tx	8 Weeks Post Induction Tx	D1	D8 and D15	D1	D15	D1	D+4 weeks post combination Tx		3 M	6, 9, 12, 15, 18, 21 & 24 M	30 M+ Q6M Yrs. 2-5
Written Informed Consent	X																
Medical History	X						X	X		X		X		"i			
Demographics/Height/ ECG	X																
Physical Exam/Vitals Adverse Event Assessment Current Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X						X	X		X		X		X			
PET with diagnostic quality CT Assessment	X						X					X		X		X	X
Bone Marrow Biopsy	X						X							X			
Survival Status & Subsequent Therapy							X							X	X	X	X
Ublituximab - IV Weekly		X	X	X	X			X	X	X		X					
Umbralisib - Oral Daily								X	X	X	X	X					
Routine Blood Tests	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Need to TSH and fT4 Creatinine Clearance Coagulation - PT/INR and PTT Pregnancy Test HIV Testing/ Hep B/ Hep C	X																
Urinalysis	X						X							X			
Research Blood Samples for banking	X						X					X		X		X	
Tumor Tissue Review	X																
Questionnaire	X						X					X		X		X	

Abbreviations: C = cycle; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HIV = human immunodeficiency virus; IV = intravenous; fT4 = free thyroxine ; M = month; PET = positron emission tomography; PT/INR = prothrombin time and international normalized ratio; PTT = partial thromboplastin time; TSH = thyroid stimulating hormone; Tx = treatment.

a.. Ublituximab will be administered every cycle (28 days) through Cycle 6, and then every 3 cycles (i.e. at Cycle 9 and Cycle 12).

How long will I be in the study?

You may continue receiving study drugs for up to 12 cycles (approximately 6 months) and be followed every 6 months for the next 2-5 years.

What are the possible discomforts or risks?

Given that this combination of therapy is currently considered experimental, it may not improve treatment outcomes, and there is a chance it could increase side effects or worsen cancer recurrence risk.

There is a risk that if the combination of treatments being tested in this study caused severe side effects. If the treatment being tested in this study was found to be less effective than current standard of care, it could reduce the chance of cancer cure, or increase risk of cancer **death**.

You may have side effects while you are in this study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study treatment that are unknown at this time. You should tell the study doctor about anything that is bothering you or any side effects that you have, even if you do not think they are related to the study treatment. Many side effects go away shortly after the medications are stopped, but in some cases side effects can be serious, long lasting, permanent, or lead to **death.**

You should talk to your study doctor about any side effects or discomfort you may have. The study doctor may give you some medicine that will help with some side effects. The study doctor may also interrupt or discontinue the study drugs or study procedures.

Risks of the Study Drugs

Risks of Ublituximab

Very Common (more than 10% of people):

- Decreased number of white blood cells that fight infection, decreased number of platelets that help with clotting
- Fever
- Infusion related reaction
- Headache

Common (greater than or equal to 2% to less than 10% of subjects):

- Decreased number of red blood cells, decrease in red blood cells, white blood cells and platelets all at the same time
- Diarrhea, pain in the abdomen, nausea or feeling queasy, itching in the mouth
- Tiredness, weakness, chills, swelling of the hands and/or feet, pain
- A liver disease causing cell destruction
- Shingles
- Increase in liver enzymes, elevated bilirubin
- Muscular weakness
- Change in taste
- Irritation in the throat, tightness in the throat
- Itching, sweating more than usual
- High blood pressure

Although rare, the following cases have been reported in subjects treated with ublituximab:

- Drug-induced hepatitis (inflammation of the liver due to toxic exposure to medication)
- Allergic reaction
- Erythrodermic eczematous rash (itchy, red and peeling rash that can be fatal)
- Malignant melanoma (skin cancer)
- Tumor lysis syndrome (a serious metabolic disorder caused by the breakdown of cancer cells and their release in the bloodstream)
- Progressive multifocal leukoencephalopathy (a serious brain infection that can lead to severe disability and **death**)
- Hepatitis B reactivation, an infection of the liver in people who have a history of hepatitis B infection, which may include symptoms such as yellowing of the eyes or skin, pain on the right side of the abdomen below the ribs, indigestion, loss of appetite, dark-colored urine often accompanied by lighter-than normal colored stools, nausea, vomiting or fatigue, and may be life-threatening or lead to **death**.

Serious infections including life-threatening and **fatal** cases have been observed in studies with ublituximab taken alone. Contact your study doctor immediately if you have any of the following signs or symptoms that may be associated with an infection:

- changes in body temperature
- fever
- chills
- nausea or vomiting
- cough
- shortness of breath
- body ache
- weakness or fatigue
- stiff neck
- confusion

- sensitivity to light

Risks of Ublituximab+Umbralisib Combination

<u>Very Common</u> (<u>greater than or equal to</u> 10% of people):

- Decreased number of red blood cells, decreased number of white blood cells
- Diarrhea, nausea or feeling queasy, vomiting, constipation
- Tiredness
- Infusion related reaction
- Decreased appetite
- Insomnia (trouble sleeping)
- Chills, fever
- Cough, headache, dizziness
- Upper respiratory infection, lung infection (pneumonia)
- Inflammation or pain that comes from inside a joint, back pain
- Abdominal pain
- Swelling of your lower legs or hands
- Sensation of difficult or uncomfortable breathing
- Low potassium levels in the blood
- Increase in liver enzymes (alanine aminotransferase and aspartate aminotransferase) found in the blood (indicates damage to the liver)

<u>Common</u> (1% to less than 10% of people):

- Decreased number of platelets
- Decrease in the hearts ability to pump blood
- Ear congestion, feeling discomfort in the ear
- Paleness in the lining of the eye, infection in the eye, eye swelling, blurred vision
- Discomfort in the abdomen, swollen abdomen, pain in the abdomen, constipation, indigestion, passing gas, gastric reflux, blood in stool, increase production of saliva, inflammation in the mouth
- Weakness, swelling of the face, pain at the site of the infusion, swelling in one area, inflammation throughout the entire body
- Increase in level of bilirubin in the blood
- Low levels of all types of gamma globulins (proteins) in the blood
- Inflammation of the lungs (bronchitis), infection under the skin, inflammation of the large intestine caused by a bacteria that can cause severe diarrhea, infection and swelling of the small and large intestine, fungal infection in or around the mouth, herpes in or around the mouth, ear infection, , common cold, infection in your blood stream that may cause your organs to fail, inflammatory response throughout the body that can cause organs to fail, sinusitis, infection of the skininfection of the urinary

tract
- Wound
- Increase in the levels of creatinine in the blood, abnormal CT scan of the chest, decrease in the proteins of the immune system, decreased weight
- Dehydration, failure to thrive, high levels of sugar in the blood, high levels of uric acid in the blood, low levels of potassium in the blood, low levels of phosphate in blood which may lead to bone weakness
- Swelling in the joints, involuntary muscle movements, muscular weakness, pain in the muscles, pain in the arms and/or legs
- Change in taste, lacking energy, sinus headache, sleepiness
- Agitation, anxiety
- Having a sudden urge to urinate, decreased kidney function, a sudden decrease in kidney function
- Scrotal cyst, discolored semen
- Choking, difficulty speaking, shortness of breath, bloody nose, low levels of oxygen in the blood, pain in the throat, inflammation of the lungs, cough that produces mucus, sinus congestion
- Hair loss, cold sweat, areas on the skin that look like acne, blistering of the skin, dry skin, bleeding under the skin, itching, flat or raised red bumps on the skin, redness on the cheeks and nose, hives
- High blood pressure

Although rare, the following side effects have been reported in subjects treated with umbralisib and/or ublituximab:
- ileus (inactive bowel)
- pulmonary edema (excess fluid in the lungs)
- drug-induced hepatitis (inflammation of the liver due to toxic exposure to medication)
- allergic reaction
- erythrodermic eczematous rash (itchy, red and peeling rash that can be fatal)
- malignant melanoma (skin cancer)
- tumor lysis syndrome (a serious metabolic disorder caused by the breakdown of cancer cells and their release in the bloodstream)
- progressive multifocal leukoencephalopathy (a serious brain infection that can lead to severe disability and **death**)

Serious infections including life-threatening and fatal cases have been observed in studies with ublituximab taken in combination. Contact your study doctor immediately if you have any of the following signs or symptoms that may be associated with an infection:
- changes in body temperature
- fever
- chills
- nausea or vomiting
- cough

- shortness of breath
- body ache
- weakness or fatigue
- stiff neck
- confusion
- sensitivity to light

Risks of the Study Procedures

Blood collection
Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to, fainting, bleeding, bruising, discomfort, dizziness, infection and/ or pain at the puncture site.

Having an IV inserted in your vein
In this study we will insert a needle, connected to a plastic tube, into a vein in your arm. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising

where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for about four or five hours.

Catheter Placement
Study drugs may be given through a central venous catheter (sometimes called a 'central line' or 'port'). If you do not already have a catheter in place, we will place one in your chest. A catheter is a plastic tube. We will also use your catheter to take blood and give you fluids

Bone marrow biopsy
In this study we will take three samples of bone marrow from your pelvic bone. Before we take each sample, we will give you some numbing medication on the skin outside your pelvic bone (on your hip). After your skin is numb, we will push a special needle into the center of your pelvic bone. Then, we will draw the bone marrow up into the syringe. When we do this, you will have a pulling feeling as the marrow leaves the bone and goes into the syringe. The area around the bone will be sore for a few days. There is a very small chance that you will be allergic to the numbing medicine. There is also a very small chance that you could bleed or develop an infection.

Electrocardiogram (ECG)
An electrocardiogram (ECG) is a test that records the electrical activity of the heart. Skin irritation is rare but could occur during an ECG from the electrodes or the gel that is used.

Imaging (PET, CT scans)

Procedures such as CT scans, X-rays and/or radioactive drugs will be used during this research study to see how you are doing. The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect you or your disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to your risk of injury or disease. When deciding to enter this study, think about your past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment.

Reproductive Risks

While participating in this research study, you should not become pregnant, nurse a baby, or father a baby. Both men and women who are able to have children must use a highly effective means of birth control approved by your study doctor.

If you are a female who has stopped having menstrual periods for at least 1 year (menopause), please discuss with your study doctor the need for birth control. If you become pregnant, you must stop taking the study drugs at once and notify your doctor immediately. You will not be allowed to continue in the study. You may be asked questions about the outcome of your pregnancy and the baby.

You must continue the use of birth control during the entire time of your study participation and to at least 120 dayss after the last dose of Umbralisib or Ublituximab, whichever is later.

If you are a male, you are responsible for informing your partner(s) that the effects of Ublituximab and Umbralisib on an unborn fetus or embryo in humans are unknown. You and your partner(s) are responsible for using acceptable birth control as described above. Discuss with your partner acceptable forms of contraception. If your partner becomes pregnant while you are on study, you must notify your doctor immediately. You and your partner may be asked questions about the outcome of the pregnancy and the baby. Written informed consent for release of medical information from your partner will be obtained prior to collecting any information about the pregnancy and baby.

Risks associated with HIV and/or Hepatitis B & C testing

If you test positive for HIV (Human Immunodeficiency Virus) and/or Hepatitis in this study, we must report your name to the Colorado Department of Public Health and Environment.)

Risk of Loss of Confidentiality

There is a risk that people outside the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the two study drugs. The study is not designed to improve your health. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks. **Are there alternative treatments?**

There may be other ways of treating your cancer. Instead of taking part in this study:

- You may choose to receive treatment with an approved therapy. Standard of care therapies for FL and MZL include antibody therapy like rituximab or chemotherapy like cyclophosphamide, vincristine and prednisone; and rituximab and bendamustine.
- You may choose to participate in a different study with another experimental drug.
- You may choose to receive comfort/palliative care.
- You may choose to get no treatment at all

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

TG Therapeutics manufactures and will provide the two drugs, Ublituximab and Umbralisib, used for the study. This research is being conducted by Dr. Manali Kamdar. The research study will only pay for procedures not considered standard of care.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

The drug manufacturer, TG Therapeutics, will pay for the cost of the study drugs, Ublituximab and Umbralisib. The funding for this study will also pay for any tests or procedures that are related to the research study.

There are some medical procedures that you would get for your condition whether you were in this study or not, such as clinic visits, diagnostic and lab tests, and imaging. These are considered standard of care. You and/or your health insurance may be billed for the costs of medical care during this study if these expenses are related to standard of care procedures. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or you do not have insurance, these costs will be your responsibility.

Ask your study doctor to discuss the costs that will or will not be covered by this research study. This discussion should include the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Kamdar immediately. Dr. Manali Kamdar at 720-848-0752 (office hours) or 303-266-2519 (24 hour contact number).

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Manali Kamdar, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Manali Kamdar at 720-848-0752 (office hours) or 303-266-4162 (24 hour contact number). You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Kamdar with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Optional Consent for Specimen Banking for Future Research

Dr. Kamdar would like to keep some blood, tissue from biopsies, and/or archived tissue that was taken during previous biopsy procedures. If you agree, the samples will be kept

and may be used in future research to learn more about cancer. The research that is done with your samples is not designed to specifically help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your samples will not affect your care.

The choice to let Dr. Kamdar keep the tissue samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your samples can be kept for research, you can change your mind at any time and contact your study doctor to let him know that you do not want Dr. Kamdar to use your samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Kamdar decides to destroy them.

When your samples are given to other researchers in the future, Dr. Kamdar will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). If your samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your samples will only be used for research and will not be sold. The research done with your samples may help to develop new products in the future, but there is no plan for you to be paid.

Because your genetic information is unique to you, there is a small risk that someone could connect the information back to you. Also, genetic research and broadly sharing data may involve risks to you or people like yourself that are unknown at this time.The possible benefits of research from your samples include learning more about what causes cancer and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Kamdar will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Kamdar.

Please read each sentence below and think about your choice. After reading each sentence, circle “yes” or “no.” If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your samples, you may still take part in the study.

I give my permission for my blood and tissue to be stored in a central tissue bank for future use by the study investigators:

1. I give my permissions for my blood and tissue samples to be kept by Dr. Kamdar for use in future research to learn more about how to prevent, detect, or treat lymphoma.

   ☐ Yes ☐ No _____Initials

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Manali Kamdar, MD
Anschutz Medical Campus
1665 N. Aurora Court
Mail Stop F754
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- TG Therapeutics, Inc. is the manufacturer of Ublituximab and Umbralisib and is also providing a grant of funding support.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.
- Tissue samples and the data with the samples.
- Billing or financial information.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or

the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.

- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures –In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

Some of these optional procedures may involve genetic testing or the use of your genetic information. Your genetic information will not be released to others. If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records.

I agree to participate in this study. My participation is voluntary and I do not have to sign this form if I do not want to be part of this research study.

Subject Signature:_____ Date: _____

Subject Print Name:_____

Consent form explained by:_____ Date: _____

Print Name: _____

---------- ***Use Only if Applicable*** ----------

Signature Line for witness; required for consent of non-reading subjects and consent using a short form, if you requested such consent procedures

Witness of Signature ☐
Witness of consent process ☐

Witness Signature:_____ Date:_____

Witness Print Name: _____