COVER LETTER

Protocol Title: Phase II study of umbralisib plus ublituximab (U2) after CLL progression on targeted therapy

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This trial is supported by TG Therapeutics, Inc. (Tracking Number: U2-NTG-004)

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Confidentiality Statement

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Protocol Summary

Title: Phase II Study of umbralisib plus ublituximab (U2) after CLL progression on targeted therapy	
Study Drugs:	Umbralisib Ublituximab
Indication:	BTK or BCL-2 inhibitor Resistant CLL
Study Phase:	Phase II
Subjects to be enrolled:	24 subjects Cohort A Post BTKi Therapy: 12 Subjects Cohort B Post BCL-2 Therapy: 12 Subjects

Background and Rationale:

Novel agents have permanently altered therapeutic strategies in patients with chronic lymphocytic lymphoma (CLL). In relapsed settings, Bruton's tyrosine kinase (BTK), B cell lymphoma-2 (Bcl-2) and Phosphatidylinositol 3 kinase delta (PI3Kδ) inhibitors have proven efficacy and garnered FDA approval in multiple therapeutic settings. Each drug demonstrates unique toxicities, efficacy, drug-drug interactions and monitoring schedules, making patient and disease specific characteristics important to consider when prescribing a particular therapy. For CLL, ibrutinib, a BTK inhibitor (BTKi), has become a standard of care for frontline therapy and is commonly the first line novel agent in patients with relapsed or refractory disease, owing to its ease of administration, safety profile, and durable efficacy[1-3]. Venetoclax, a Bcl-2 inhibitor, has also been shown to be safe and effective in salvaging BTKi resistant disease and is now approved as a frontline therapy in combination with obinutuzumab and for patients with relapsed CLL after 1 prior line of treatment in combination with rituximab [4-6]. Its use is complicated by a potential for life threatening tumor lysis which requires an intensive monitoring program during initiation and dose escalation, which can be burdensome to patients and physician practices, and may limit its widespread use outside of academic centers. Lastly, the use of PI3Kδ inhibitors such as idelalisib or duvelisib, have been relegated to third or fourth line treatment options largely due to historically inferior efficacy and toxicity secondary to increased infectious risks and autoimmune complications such as colitis, pneumonitis and hepatitis [7, 8].

Despite the increasing numbers of therapeutic options, the optimal sequencing of therapies remains unknown with only limited retrospective data available estimating therapeutic benefit of each class of drug after progression on a BTKi.

Umbralisib, a PI3Kδ inhibitor, has proven safe and effective in relapsed disease when combined with ibrutinib and or ublituximab [9, 10]. Umbralisib is built on a different chemical backbone than previous PI3Kδ inhibitors such as idelalisib and duvelisib, and to date has demonstrated a significantly improved safety profile making it an attractive option as a salvage regimen in patients with BTK or BCL2 resistant disease.

Methodology:

We propose a single center Phase II study to evaluate the efficacy and safety of umbralisib and ublituximab (U2) as salvage in patients with CLL who have progressed either on a BTK inhibitor or BCL-2 inhibitor. The study will enroll in two parallel cohorts and subjects will be assigned based on which class of novel agent containing regimen was used prior. **Cohort A** will consist of patients who progress after BTKi containing regimens and **Cohort B** will consist of patients who progress after a BCL-2 containing regimens. Subjects who progress on a regimen containing both a BTKi and a BCL-2 inhibitor, will be enrolled in cohort B. Each cohort will be evaluated independently of each other.

Objectives:

Primary Objective: The primary objective of this study will be to evaluate the overall response rate (ORR) of umbralisib in combination with ublituximab in patients with CLL who have progressed on a BTK or BCL-2 inhibitor.

Secondary Objectives: Secondary objectives will be to evaluate complete remission rate, duration of response and safety.

Exploratory Objectives: Progression free survival (PFS) and overall survival (OS) will be assessed as exploratory objectives. We will also be collecting samples for future use in research as yet undetermined subject to review and approval by TG Therapeutics, Inc. Potential correlative studies may evaluate molecular predictors of response or resistance, changes in immune profile, and clonal evolution patterns in patients exposed to U2.

Drug Administration and Study Schedule:

Subjects that meet eligibility criteria will be enrolled and initiate therapy with umbralisib monotherapy for a one cycle lead in Cycle -1. During this lead in cycle of 28 days subjects will initiate umbralisib monotherapy at 800mg orally daily. Starting at C1D1 subjects will initiate combination therapy with U2, on 28 day cycles. During combination therapy, starting cycle 1 subjects will be treated with umbralisib 800mg orally daily and continue daily dosing through all subsequent cycles. Ublituximab will be co-administered on days 1 and 2 (split over days 1 and 2), 8, 15 of Cycle 1 then on D1 for subsequent cycles 2-6. After cycle 6, combination therapy will be completed and subjects will continue with monotherapy umbralisib daily. Subjects will be eligible for response assessment if they complete two cycles of therapy or are noted to have documented clinical progression of disease prior to first study mandated radiographic assessments. Radiographic evaluation for response will occur prior to C3, then occur prior to C7D1 and then every 6 months for up 2 years. Subjects who remain on study after two years will be radiographically evaluated annually thereafter until complete remission or upon evidence of clinical progression. Subjects that have achieved a CR will be followed clinically with physical exam and labwork but will not be required to undergo routine scanning. Study visits will occur monthly on D1 for Cycles 1-7 then every 3 months thereafter as long as patient continues to have clinical benefit.

Subject Selection:

Inclusion Criteria:

A subject will be eligible for participation in the study if he/she meets the following criteria:

1. Subject must have confirmed diagnosis of CLL/SLL and a treatment indication based upon 2018 International Workshop on CLL (IWCLL) criteria.
2. Subject must have documented disease progression on a BTK and or BCL-2 containing regimen as the most recent prior line of therapy. Subjects who were treated with a regimen containing both classes of novel agents will be allowed to enroll and will be enrolled into Cohort B. Subjects who receive a temporizing non-experimental treatment such as monotherapy with an anti-CD20 monoclonal antibody or corticosteroids including high dose methylprednisolone for up to 2 cycles immediately after progression on a BTK or BCL-2 inhibitor will be considered for enrollment after discussion with the study sponsor.
3. Subject must be ≥18 years of age.
4. Subject must have an Eastern Cooperative Oncology Group performance status of ≤2.
5. Subject must have adequate bone marrow function to meet the below thresholds.
    a. Absolute neutrophil count of >750 cell/μL in absence of G-CSF for 7 days prior to screening.
    b. Platelet count of ≥ 30,000 cells/μL independent of transfusion for 21 days prior to enrollment
6. Subject must have adequate organ function and meet the thresholds below:
    a. Total bilirubin ≤ 1.5 times the upper limit of normal (ULN). Subjects with bilirubin exceeding this limit due to Gilbert's disease are eligible.
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement.
    c. Creatinine clearance >30 ml/min/1.73m^2 as calculated by the MDRD equation.
7. Ability to swallow and retain oral medication.
8. Female subjects who are not of child-bearing potential (see Appendix: CONTRACEPTION GUIDELINES AND PREGNANCY), and female subjects of child-bearing potential who have

a negative serum pregnancy test within 3 days prior to initial trial treatment. Male subjects of reproductive potential may not participate unless they agree to use medically acceptable contraception. Female subjects of child-bearing potential and all male partners, and male subjects must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of study drug.

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

Exclusion Criteria:

A subject will be ineligible for the study if he/she meets any of the following criteria:

10. Subject has had prior exposure to a PI3K inhibitor at any point in treatment history.
11. Subject has discontinued the BTKi or BCL2 due to intolerance. Intolerance will be defined as discontinuing prior BTKi or BCL2 therapy for any reason without evidence of progression. Subjects who were re-challenged after discontinuation for therapeutic reasons will be allowed if the toxicity did not recur or was managed without indication for discontinuation. Subjects who progress on BTKi or BCL2 therapy who were on a reduced dose due to an AE/intolerance are eligible as long as progression has been documented on that reduced dose.
12. Subject has history of or clinical or radiographic evidence of, or has biopsy proven Richter's transformation or prolymphocytic leukemia.
13. Subject has undergone an allogeneic stem cell transplant.
14. Subject has received an autologous hematologic stem cell transplant within 6 months of study entry.
15. Malignancy within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry.
16. Subject is known to be positive for HIV.
17. Subject has history of hepatitis C infection, active infection with hepatitis B or active cytomegalovirus (CMV) as determined by positive PCR.
18. Previous exposure to BTK or Bcl-2 inhibitor therapy within 14 days of initiating study treatment on Cycle - 1 Day 1, or previous exposure to anti-cancer therapy including chemotherapy, radiotherapy, or investigational therapy, including other investigational targeted small molecule agents within 21 days of initiating study treatment on Cycle 1 Day 1.
19. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails.
20. History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 administration.
21. A known history or active autoimmue disease even if not requiring systemic immunosuppression. Subjects with known history of immune thrombocytopenic purpura or autoimmune hemolytic anemia secondary to CLL are allowed to enroll.Malabsorption syndromes
22. Irritable bowel syndrome with greater than 3 loose stools per day as a baseline.
23. Any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
    a. Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV [see Appendix: NYHA Classifications])
    b. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, CHF, or myocardial infarction within 6 months of enrollment.
    c. Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.

d. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), symptomatic peripheral arterial disease, angioplasty, cardiac or vascular stenting within 6 months of enrollment.

24. Females who are pregnant or lactating.

Statistical Analysis Plan:

Currently available retrospective evidence demonstrates an ORR of ~35-40% when idelalisib is used as first salvage after ibrutinib failure [11]. Given umbralisib's unique molecular properties and combination therapy with ublituximab, we hypothesize a response rate of 55% using U2 as first salvage. Salvage rates with novel agents after venetoclax failure in subjects considered double refractory are unknown. We anticipate close to 90% of patients enrolled in cohort B will have double refractory disease and represent a high risk group. Given these limitations, we anticipate a response rate of 40% in this group based off the efficacy seen with idelalisib after ibrutinib failure.

Because this is a pilot study, no formal sample size/power calculation is required. Given the anticipated different patient populations in each cohort, no cross cohort comparisons will be performed. However, with 12 patients enrolled in cohort A, an exact binomial (Clopper-Pearson) 95% confidence interval for the overall response rate can be constructed to have a width of approximately 57.6% (25.0%, 82.5%). This calculation assumes that the overall response rate will approach 55% in cohort A.

Similarly, with 12 patients enrolled in cohort B, an exact binomial (Clopper-Pearson) 95% confidence interval for the overall response rate can be constructed to have a width of approximately 56.9% (14.1%, 70.9%). This calculation assumes that the overall response rate will approach 40% in cohort B.

Given this is a pilot study with low subject enrollment with lack of power, analysis of outcomes will remain descriptive. Assuming adequate follow-up time, Kaplan-Meier survival analysis will be used to assess, progression-free survival (PFS), and overall survival (OS), in the entire cohort. All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for 1) the overall response rate, 2) median PFS/OS-time, and 3) PFS/OS proportions, will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and Stata Version 15.0 (StataCorp, College Station, TX).

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1. Study Objectives

The objective of this study is to assess the efficacy and safety of umbralisib in combination with ublituximab (U2) in patients after progression on Bruton's tyrosine kinase (BTK) or B-cell lymphoma-2 (Bcl-2) inhibitors.

1.1. Primary Objectives

Primary Objective: The primary objective of this study will be to evaluate the overall response rate (ORR) of umbralisib plus ublituximab in patients with CLL who have progressed on a BTKi or BCL-2 inhibitor.

1.2. Secondary Objectives

Secondary Objectives: Secondary objectives to be evaluated in the study will be complete remission rate, duration of response, and safety.

1.3 Exploratory Objectives

Exploratory Objectives: Progression free survival (PFS) and overall survival will be exploratory objectives. We will also be collecting samples for future use in research as yet undetermined subject to review and approval by TG Therapeutics, Inc. Potential correlative studies may evaluate molecular predictors of response or resistance, changes in immune profile, and clonal evolution patterns in patients exposed to U2.

2. Background

2.1 Disease

Chronic lymphocytic leukemia (CLL) is one of the most common leukemias diagnosed in the United States with approximately 20,000 new cases each year [12]. The median age at diagnosis is 71 and follows an indolent and prolonged asymptomatic interval for the majority of patients. Symptomatic disease is characterized by the increased accumulation of leukemic cells in the peripheral blood, spleen, lymph nodes and bone marrow which lead to B symptoms, bulky adenopathy, splenomegaly and the onset of cytopenias. Early studies have shown that early intervention with treatment at diagnosis could not meaningfully impact patient survival and thus upon diagnosis patients are actively monitored until symptoms of the disease manifest [13].

Over past the 20 years there has been numerous prognostic factors that impact outcomes to standard CIT regimens. Specifically IGHV mutational status and cytogenetic abnormalities have the ability to identify patients at risk of early progression or who will have inferior outcomes with chemo immunotherapy [14-16]. Increasingly mutational data has identified patients at high risk of failure to CIT regimens with mutations in *SF3B1, NOTCH1, TP53, BIRC3* and *EGR2* independently predicting early progression and or poor outcomes to standard chemo immunotherapy (CIT) regimens [17-21].

Given the early and long term toxicities associated with CIT and the significant proportion of patients that have poor outcomes when used in salvage settings highlights an important unmet need in the treatment of patients with CLL. The advent of novel therapies such as BTK, PI3 kinase δ and Bcl-2 inhibitors have provided durable and effective therapies for patients with high risk disease that have failed standard CIT regimens [2, 22, 23]. Importantly the BTK inhibitor ibrutinib is approved for frontline treatment by the Federal Drug Administration for patients with CLL providing the first upfront small molecule therapy for all patients with CLL [1].

Current management trends for CLL are moving away from CIT based therapy to upfront therapy with novel agents such as ibrutinib. Combination BTK and BCL-2 inhibitors that may provide prolong treatment free intervals and deep remissions and are currently being tested in frontline and relapsed settings. Upon relapse it remains unknown how patients will respond to repeated courses of these agents and or whether prolong durable disease control can be achieved with repeated courses of novel therapies. In relapsed previously treated settings, despite the use of these agents, patients with high risk disease still remain at risk for progression and thus represent a shifting unmet need [24]. There remains an ongoing need for additional agents and combinations of treatments with non-overlapping toxicities and unique mechanisms of action.

2.2 Rationale

In relapsed settings, BTK, BCL-2 and PI3Kδ inhibitors have proven efficacy and are FDA approved in multiple therapeutic settings. Each class of drug demonstrates unique toxicities, efficacy, drug- drug interactions and monitoring schedules, making patient and disease specific characteristics important to consider when prescribing a particular therapy. Ibrutinib, BTKi, has become a standard of care for frontline therapy and is commonly the first line novel agent administered in patients with relapsed or refractory disease, owing to its ease of administration, safety profile, and durable efficacy [1, 2, 25]. Venetoclax, a Bcl2 inhibitor, has also been shown to be safe and effective in salvaging BTK resistant disease but currently is only approved for use in 17p deleted relapsed/refractory settings with likely broader approval for use after 1 prior therapy in 2018 based on the Murano study [4, 5]. Its use is complicated by a potential for life threatening tumor lysis which requires an intensive monitoring program upon drug initiation and escalation, which can be burdensome to patient and physician practices and may limit its widespread use outside of academic centers. Lastly, the use of PI3Kδ inhibitors such as idelalisib, have been relegated to third or fourth line treatment options largely due to efficacy and toxicity secondary to increased infectious risks and autoimmune complications such as colitis, pneumonitis and hepatitis. Despite multiple therapeutic options the optimal sequencing of therapies remains unknown with only limited retrospective data available estimating therapeutic benefit of each class of drug after progression on a BTKi [26].

Umbralisib, a PI3Kδ inhibitor, has proven safe and effective in relapsed disease as a monotherapy and when combined with ibrutinib and or ublituximab [9, 10, 27]. Umbralisib has well documented safety profile which differs from previous PI3Kδ inhibitors making it an attractive option as a salvage regimen in patients with BTK resistant disease in that it does not require an intensive monitoring program upon drug initiation or inpatient hospitalization. Ublituximab is a novel anti-CD20 antibody that has proven safe and effective in rituximab treated patients as monotherapy and also in combination with novel agents [28-30]. Additionally, for patients that

have progressed on venetoclax and ibrutinib, idelalisib remains an option for salvage though this is complicated by toxicities and the effectiveness of PI3Kδ inhibitors in this setting is unknown. We propose a multi-center Phase II study to evaluate the efficacy and safety of umbralisib and ublituximab (U2) as salvage in patients with CLL who have progressed either on a BTK or BCL-2 inhibitor.

2.3 Investigational Agents - Umbralisib

2.3.1 Umbralisib

Umbralisib is a highly specific and orally available PI3Kδ inhibitor with nanomolar inhibitor potency and high selectivity for delta compared to alpha, beta, and gamma isoforms with a delta IC50 of 22.23 nM compared to >10,000, 1,116, and 1065nM respectively for alpha, beta and gamma isoforms. 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 are strongly implicated in various hematologic malignancies.

2.3.2 Umbralisib Non-Clinical Studies

The potency and specificity for PI3kδ has been evaluated in both *in vitro* and *in vivo* models. Data from a homogenous time resolved fluorescence (HTRF) based enzyme assay demonstrated the specificity of umbralisib to PI3kδ with >1000, 50 and 48 fold selectivity for δ over α, β, and γ isoforms respectively indicating the primary mode of action is via inhibition of the δ isoform.

To confirm potency and selectivity for the PI3Kδ isoform, inhibition of CD63 activation whole blood was determined. Samples were collected from healthy volunteers and treated with vehicle or increasing concentrations of compound prior to activation of fMLP and FcεR1 signaling, which is mediated through PI3K γ and δ isoforms respectively. By measuring CD63 surface expression the EC 50 was 3274nM and 66.22nM after activation via fMLP and FcεR1 respectively, demonstrating selectivity of umbralisib for the δ isoform.

Umbralisib has been tested in an LPS induced human whole blood proliferation assay with data suggesting that 100-1000nM concentration is sufficient to cause inhibition of B cell proliferation by 50-80%. Additionally, this finding was confirmed using a similar proliferation assay in the mouse demonstrating a slightly lower potency with only 50% reduction in proliferation at 1000nM. This was confirmed with *in vivo* experiments in mice pretreated with increasing concentrations of umbralisib which indicated that a circulating plasma concentration of ~3μM was necessary to cause arrest of B cell proliferation by 50% in normal mice.

Similarly, inhibition of LPS-induced AKT phosphorylation was determined *ex vivo* using isolated mouse splenocytes. In these studies umbralisib caused a dose dependent reduction in phosphorylation of AKT.

Next proliferation of immortalized leukemic cells representative different hematologic malignancies were treated with umbralisib demonstrating different potencies (Study No. IVT-5264-

LCA-01). Overall 50% growth inhibition for the majority of B, T, and monocytic cell lines was achieved at concentrations of 0.5-7.5 μM of umbralisib.

Lastly the activity of umbralisib was tested *in vivo* within an adoptive transfer eu-TCL1 mouse model of CLL (Maharaj et al IWCLL 2017). In these studies umbralisib was compared to duvelisib and idelalisib. Anti-tumor activity was similar between all three molecules. Umbralisib was found to have less effect on Treg numbers comparatively to the two other drugs. Umbralisib mice experienced significantly lower incidence of severe adverse events compared to duvelisib mice. Additionally duvelisib combined with a CK1e-inhibitor was able to partially restore Treg numbers suggesting CK1ε inhibition by umbralisib may influence Treg survival.

2.3.3 Non-Clinical Pharmacokinetics

Pharmacokinetic studies following single dose and repeat dose administration were performed in mice, rats, dogs and cynomolgus monkeys. Except for a P-gp inhibitory potential, the results demonstrated no DDI effects against major CYPs, conjugating enzymes, and transporters evaluated.

Absorption of umbralisib was rapid with peak concentrations (Tmax) achieved within 2 hours after oral dosing in all species with moderate clearance. Oral bioavailability was approximately 30-50% in all species except in rats where oral bioavailability was >90%. Elimination half-life (T1/2) was 5.26 hours in mice, 1.59 hours in rats, 3.21 hours in monkeys and 20.63 hours in dogs.

The primary elimination route after oral administration was found to be fecal with no detectable levels found in urine upon single dose administration in rats.

2.3.4 Non-Clinical Toxicity

In acute single dose oral toxicity studies, umbralisib was well tolerated at a dose of 2000 mg/kg in male and female rats. The animals tolerated 2000mg/kg with no adverse findings with no mortality observed after 14 days of observation. In mice umbralisib was well tolerated at a dose of 1000mg/kg though mortality was observed in the confirmatory single dose study of 1000mg/kg and 2000mg/kg. Less than 500mg/kg was found to be tolerated in the study.

In a 28 day repeated dose study performed in CD1 mice, no umbralisib-related mortality occurred during the study. Umbralisib treatment related effects found in clinical pathology were slight decreases in leukocytes and lymphocytes at 750mg/kg/day, increases in cholesterol at 150 and 750mg/kg/day and increases in AST, ALT and GGT at 750mg/kg/day in female mice only. After a 14 day recovery period there was complete recovery of organ weight changes and microscopic findings of liver abnormalities noted in female mice. Based on these studies the no-observed-adverse-effect-level (NOAEL) was considered to be 150mg/kg/day.

A similar study with repeated dosing was performed in dogs. Umbralisib treatment related clinical effects were observed in dogs dosed at 655 and 196.5 mg/kg/day consisting of dehydration, diarrhea, vomiting, and ocular discharge. Based on severity, 3 animals were euthanized and the remaining animals had doses reduced. After reduction of dosing, treatment related clinical effects were seen primarily at 400mg/kg/day including diarrhea, vomiting, ocular

discharge and partial palpebral closure. Once daily oral administration in dogs was well tolerated in dogs at levels of 50 and 150mg/kg/day with the GI tract being the target organ system based on clinical signs and symptoms. The NOAEL was determined to be 150mg/kg/day.

2.3.5 Umbralisib Clinical Pharmacokinetics/Pharmacodynamics

Two healthy subject bioequivalence studies have been completed. The first study, TGR-1202-PK 101, was performed to assess the mean plasma concentration of umbralisib over time. In general, administration of umbralisib under fed conditions results in a higher rate of exposure relative to when the drug was administered in fasting conditions. Food increased both the extent and rate of exposure of umbralisib. The peak plasma levels of umbralisib increased by over 173% when administered with food. Using this data, a 334mg dose of umbralisib in fasting conditions can be extrapolated to an oral dose of 200mg of umbralisib under fed conditions.

The second bioequivalence study was performed to assess different formulations of product. The mean rate and extent of exposure to umbralisib were higher following administration of micronized drug product compared to the original drug product formulation. The peak plasma levels of umbralisib increased by over 124% following administration of the micronized drug product formulation in fasting conditions.

Pharmacokinetic sampling was performed on TGR-1202 101 in patients with relapse and refractory heme malignancies with 24 hour sampling conducted on day 1 of cycle 1 and cycle 2. Umbralisib was rapidly absorbed Tmax ~2 hours with steady state concentrations achieved by Day 15 of dosing with a half-life of ~100 hours. The improved exposure with the micronized formulation of umbralisib in the healthy volunteer study was confirmed during the Phase 1 dose escalation study with the 800mg dose demonstrating a mean Cmax of ~4500 ng/Ml with a mean steady state concentration of ~3500 ng/Ml measured 24 hours after dosing which is well above the IC90 of PI3Kδ of ~400ng/mL.

2.3.6 Umbralisib Clinical Studies

TGR-1202-101

Umbralisib has been evaluated in a single agent Phase I dose escalation study TGR-1202-101 in patients with relapsed and refractory hematologic malignancies which is published [27]. Patients were enrolled in 3+3 dose escalation design starting at 50mg daily with subsequent cohorts evaluating doses up to 1800mg daily. The primary objective was to determine the maximal tolerated dose (MTD). At the end of the study, 90 patients were enrolled with low rates of grade 3 or 4 adverse events. No significant safety concerns have been recognized or reported in the trial up through 1200mg daily of the micronized formulation. The most common treatment-emergent adverse events were diarrhea (43%), nausea (42%), and fatigue (31%) The most common grade 3 or 4 adverse events were neutropenia (13%), anemia (9%) and thrombocytopenia (7%). Serious adverse events considered at least possibly related to umbralisib occurred in seven patients: pneumonia (3%), lung infection (1%), febrile neutropenia (1%) and colitis (2%). The MTD was found to be 1200mg. A dose dependent response has been observed

with umbralisib with a dose of 800mg or higher producing significant nodal reductions among CLL patients with response rates approaching 60%.

UTX-TGR-103

Ublituximab plus umbralisib has also been studied in subjects with previously treated CLL/SLL or NHL in a Phase I/Ib study. Additionally, cohorts evaluating ublituximab in combination with umbralisib as a doublet and with ibrutinib as a triplet or in combination with ublituximab, umbralisib and bendamustine have been performed and are accruing. These studies have been presented in abstract form demonstrating durable responses and low rates of Grade 3 or 4 toxicities. Common toxicities of all grades in >20% of patients treated across all studies with the U2 combination were confined to neutropenia, nausea, diarrhea, and fatigue.

2.4 Investigational Agents – Ublituximab

2.4.1 Ublituximab

Ublituximab is a monoclonal recombinant anti-CD20 immunoglobulin, produced by a stable expression in a clone of the rat myeloma cell line YB2/0. Ublituximab displays the classic structure of IgG1 immunoglobulins. It is a chimeric antibody composed of a murine variable region fused onto a human constant region. Due to a specific glycosylation pattern of its FC region, ublituximab displays an increased affinity for the FCγRIIIa and induces a higher *in vitro* antibody dependent cellular cytotoxicity (ADCC) against B cells compared to rituximab and ofatumumab.

2.4.2 Ublituximab Non-Clinical Studies

Ublituximab specifically targets human CD20 antigens expressed on Raji cells with a high affinity (equilibrium dissociation constant KD= $1x10^{-8}$ and dissociates from CD20 faster than rituximab (RTX).

Exploratory investigations suggested both ADCC and complement dependent cytotoxicity (CDC) play a role in killing of B cells since ublituximab mediated lysis was inhibited by the depletion of NK cells and by complement inactivation at high antibody concentrations.

NK cells from CLL patients displayed the same cytotoxic activity against tumor cell lines suggesting the patient derived NK cells have normal capacity to be activated. In the presence of NK cells from CLL patients, ublituximab mediates more than 80% ADCC of Raji cells at the highest antibody concentration tested, 10ng/mL.

Complement dependent cytotoxicity was measured with ublituximab in Raji cells demonstrating an EC50 of 1.5 to 2 fold higher CDC activity for RTX compared with ublituximab. Similar results were seen in WIL2-S lymphoma cells.

No apoptosis was seen in ublituximab exposed cells without effector cells or complement present and direct killing from binding CD20 is not the mechanism of action of cell kill for the molecule.

In vivo CLL clearance studies have been performed and have shown complete clearance of human CLL cells injected into SCID mice at 1mg/kg at 30 minutes of administration. The clearance was complement independent as the same effect was seen in SCID-NOD mice. Additionally, its cell clearance was specific for CD20 as controls did not demonstrate CLL death.

Ublituximab efficacy versus RTX has been investigated in a xenograft follicular lymphoma model. An ublituximab dose of 100mg/kg demonstrated superior antitumor activity with a 21 delay in tumor growth compared to the same dose of RTX treated mice.

Cross reactivity studies were performed on normal adult human tissues. The study confirmed binding was restricted to CD20 expressing cells and restricted to lymphoid tissues.

2.4.3 Ublituximab Non-Clinical Pharmacokinetics

Pharmacokinetic studies following single dose administration were performed in rabbits and cynomolgus monkeys.

A single-dose pharmacokinetic study at doses of 0.3, 10, 100 mg/kg given intravenously. The mean terminal half-life was 7 days at 10 or 100mg/kg of ublituximab with Cmax of 211 and 2086 μg/mL respectively.

In single dose toxicology studies with doses up to 100mg/kg no treatment-related effects on mortality, clinical signs, body weight, food consumption, and gross necropsy. No clinically significant changes in blood chemistry values were noted on day of sacrifice.

Repeated dose toxicology studies have been performed. At 10mg/kg no clinical signs were observed. No treatment related effects on mortality, body weight, food consumption, hematology parameters, clinical chemistry or coagulation parameters were observed. At the 50mg/kg dose, two animals had shown signs of distress. Body weight loss was noted and slight reduction of food consumption were observed in males. Under the experimental conditions of the repeat dose study, the NOAEL was established at 10mg/kg

No reproductive or developmental studies have been conducted. In humans, cross reactivity studies demonstrated that no staining was observed in genital systems and it did not cross react with human placenta.

2.4.4 Ublituximab Clinical Pharmacokinetics/Pharmacodynamics

Ublituximab has been investigated in 10 sponsored clinical trials in patients with relapsed and refractory hematologic malignancies. Pharmacokinetics (PK) of ublituximab has been determined in subjects with relapsed or refractory CLL in a dose escalation Phase I study. Main PK findings demonstrated intrasubject variability for ublituximab serum concentrations over different time points and at all dose levels ranging from 10%-220%. Exposure appeared to increase more than dose proportionally with increasing dose over the tested ranges. Clearance after single and repeated infusion decreased with increasing dose thereby increasing terminal

half-life. Lastly upon additional dosing of 4 weekly doses of 450mg resulted in higher serum concentrations at Day 50 indicating accumulation of free ublituximab in serum is maintained after seven successive infusions.

Significant lymphocyte depletion was observed in all subjects reflecting the intended biological activity ublituximab. Lymphocyte depletion was maximal after the 4th dose with median depletion of 97% relative change persisting for one month. After 8 weekly doses lymphocyte depletion was unchanged but persisted for over 6 months after the last dose.

2.4.5 Ublituximab Clinical Studies Safety/Efficacy

CD20-0703

The first in human trial was initiated in November 2008 CD20-0703. Thirty-three subjects were treated which established the safety and schedule of the drug. Of the 33 subjects 45% completed all infusions. Of the 18 subjects who discontinued 13 did due to lack of efficacy, 2 due to AEs and 1 withdrew consent. A total of 332 adverse events (AEs) were experienced with 170 of them attributable to ublituximab. Of those 170 AEs, 146 occurred during the study infusion period. Drug related grade 3 and 4 events were reported in 63.6% and 27.3%, respectively most commonly related to neutropenia, infusion reactions, and elevated liver enzymes. The most frequent drug-related AEs were infusion related reactions (60.6%), pyrexia (54.5%), neutropenia (45.5%), thrombocytopenia (30.3%), headache (24.2%), chills (21.2%), elevated liver enzymes (18.2%), nausea and asthenia (12.1%).

Twenty three infusion related reactions (IRR) were reported in 20 subjects. Sixteen of the IRRs were Grade 2, and 7 were Grade 3. Sixteen of the 23 IRRs occurred after the first infusion of ublituximab, 3 after the second infusion, and 4 after subsequent infusions. Fifteen drug-related infections were reported in 9 subjects. Ten of the 15 were mild to moderate upper respiratory infections, herpes outbreaks, or anal abscesses. Grade 3 or greater infections were noted in 5 patients in heavily pretreated patients with listeriosis, pulmonary aspergillosis, varicella and staph aureus sepsis.

Regarding efficacy, no complete remissions (CR) were reported. Out of 18 evaluable patients 5 (27.5%) were in partial remission (PR) in Part I at month 4 and 7 (63.6%) were in PR in part II at month 4. Rapid and profound lymphocyte depletion was observed and sustained in most subjects. No dose limiting toxicity was reported.

UTX-TGR-103

The doublet U2 which will be utilized in this protocol has been evaluated in a Phase I/Ib trial in CLL/SLL and NHL, initially reported by (Lunning et al ASH 2015). In the doublet cohort one dose limiting toxicity (DLT) of Grade 4 neutropenia occurred in CLL cohort which later resolved in later cycles. In this study the most common AEs of Grade 3 or higher occurring in more than 3% of patients were neutropenia (28%), diarrhea (8%), abdominal pain (8%), pneumonia (8%), thrombocytopenia (4%), asthenia (4%), febrile neutropenia (4%), sepsis (4%). Grade 3 or greater IRRs were experienced in only 1% of subjects.

In the doublet cohort the combination was found to be effective with an overall response rate (ORR) of 80% in CLL/SLL patients with a 10% CR rate.

Currently a Phase III study UTX-TGR-304 Unity CLL study was initiated Feb 2016. This study is a 4 arm study evaluating the combination doublet U2 versus monotherapy umbralisib, monotherapy ublituximab, and combination obinutuzumab and chlorambucil. No results are currently available but 3 INDSRs have been reported during the trial. Anaphylactic shock, multiple organ failure and tumor lysis syndrome all of which have been closed.

Clinical data summary

Over 400 subjects have been exposed to ublituximab. Exposure has ranged in dose from 450mg to 1200mg both as induction and maintenance. The maximal tolerated dose has not been established but in oncology setting the 900mg dose has been chosen for additional studies. In all studies, infusion-related reactions were the most frequent drug-related AE, typically occurring during the first ublituximab infusion. Infusion related reaction symptoms may include, but are not limited to: chills, fever, weakness and flushing. Grade 3-4 neutropenia, rarely associated with a febrile episode, has been reported and usually resolved either spontaneously or in a few days with G-CSF support. Drug-related Grade 3 thrombocytopenia and Grade 3-4 pancytopenia has also been reported. Asymptomatic, isolated, and transient Grade 2-3 drug-related elevated liver enzymes have been observed as well. Most subjects who experience ublituximab related adverse events may have a dose interruption or delay, and usually resume at the original dose.

Seventy-five patients have been exposed to combination therapy (U2) through the ongoing Phase I/Ib clinical trials in patients with relapsed or refractory NHL or CLL as of July 2017. Twenty-eight (28%) percent of patients experienced Grade 3/4 neutropenia. No other Grade 3/4 events occurred in ≥ 10% of patients in the doublet cohort of UTX-TGR-103.

2.5 Risk/Benefit Assessment

Overall, the data from non-clinical studies in non-human species have not revealed any potentially serious toxicities that would preclude the use of umbralisib in patients with hematologic malignancies. Further, data from the ongoing studies of umbralisib has not revealed any unexpected safety trends, and umbralisib has been well tolerated up through 1200 mg QD of the micronized formulation, with patients now on umbralisib for durations in excess of four-years; however long term safety data is only available from a limited number of patients, and should therefore be cautiously extrapolated to other target populations. Considering the clinical activity demonstrated by the class of PI3Kδ inhibitors to date, along with the preliminary activity demonstrated by umbralisib thus far, in conjunction with manageable safety profile, the potential benefit-risk ratio of umbralisib is anticipated to be positive in patients with hematologic malignancies. Upon the administration of ublituximab to subjects with CD20-positive lymphoproliferative disorders, one should be aware of the AEs reported in the safety data from the completed and ongoing Phase I studies with ublituximab and the known side-effects reported thus far with other anti-CD20 monoclonal antibodies.

Preliminary safety profile of ublituximab has been inferred from two Phase I studies in advanced stage subjects with CLL and lymphoma exposed to 4 to 8 weekly infusions of the product, and from a limited number of B-Cell Lymphoma subjects exposed to ublituximab in combination with other anti-cancer agents for longer durations. It should therefore be cautiously extrapolated to other target populations and other schedules of ublituximab infusions and or combinations. Taking into account the above mentioned risks, special attention has to be focused on management of acute infusion-related reactions and monitoring of complete blood cell count in order to detect and treat if necessary early or late episodes of neutropenia. In conclusion, considering the more active pre-clinical profile of ublituximab compared with rituximab in B-cell lymphoproliferative disorders, the rapid, profound and sustained blood lymphocyte depletion, the interim assessment of response and the manageable toxicity observed in the Phase I and II studies, the potential benefit-risk ratio of ublituximab is anticipated to be positive in subjects with B-cell malignancies.

3. Subject Selection

3.1 Study Population

Subjects with a diagnosis of CLL/SLL and who have had progressive disease on either a BTK inhibitor, BCL-2 inhibitor, or combination regimen containing one or both of those two classes of drugs will be eligible for participation in this study. Subjects who have received each class of drug in any sequence will be eligible to enroll.

3.2 Inclusion Criteria

A subject will be eligible for participation in the study if he/she meets the following criteria:

1. Subject must have confirmed diagnosis of CLL/SLL and a treatment indication based upon 2018 InternationalWorkshop on CLL (IWCLL) criteria.

2. Subject must have documented disease progression on a BTK and or BCL-2 containing regimen as the most recent prior line of therapy. Subjects who were treated with a regimen containing both classes of novel agents will be allowed to enroll and will be enrolled into Cohort B.
   Subjects who receive a temporizing non-experimental treatment for up to 2 cycles such as monotherapy with an anti-CD20 monoclonal antibody or corticosteroids including high dose methylprednisolone immediately after progression on a BTK or BCL-2 inhibitor will be considered for enrollment after discussion with the study sponsor.

3. Subject must be ≥18 years of age.

4. Subject must have an Eastern Cooperative Oncology Group performance status of ≤2.

5. Subject must have adequate bone marrow function and meet the below thresholds.

a. Absolute neutrophil count of ≥ 750 cell/μL in absence of G-CSF for 7 days prior to enrollment.
b. Platelet count of ≥ 30,000 cells/μL independent of transfusion for 21 days prior to enrollment

6. Subject must have adequate organ function and meet the thresholds below:
    a. Total bilirubin ≤ 1.5 times the upper limit of normal (ULN). Subjects with bilirubin exceeding this limit due to Gilbert's disease are eligible.
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement
    c. Creatinine clearance >30 ml/min/1.73m2 as calculated by the MDRD equation.

7. Ability to swallow and retain oral medication.

8. Female subjects who are not of child-bearing potential (see Appendix: CONTRACEPTION GUIDELINES AND PREGNANCY), and female subjects of child-bearing potential who have a negative serum pregnancy test within 3 days prior to initial trial treatment. Male subjects of reproductive potential may not participate unless they agree to use medically acceptable contraception. Female subjects of child-bearing potential and all male partners, and male subjects must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of study drug.

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

3.3 Exclusion Criteria

A subject will be ineligible for the study if he/she meets any of the following criteria:

1. Subject has had prior exposure to a PI3K inhibitor at any point in treatment history.

2. Subject has discontinued the BTK or BCL2 inhibitor due to intolerance. Intolerance will be defined as discontinuing prior BTKi or BCL-2 therapy for any reason without evidence of progression. Subjects who were re-challenged after discontinuation for therapeutic reasons will be allowed if the toxicity did not recur or was managed without indication for discontinuation. Subjects who progress on BTKi or BCL-2 therapy who were on a reduced dose due to an AE/intolerance are eligible as long as progression has been documented on that reduced dose.

3. Subject has clinical or radiographic evidence of, or has biopsy proven Richter's transformation or prolymphocytic leukemia.

4. Subject has undergone an allogeneic stem cell transplant.

5. Subject has received an autologous hematologic stem cell transplant within 6 months of study entry.

6. Malignancy within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry.

7. Subject is known to be positive for HIV.

8. Subject has history of hepatitis C infection, active infection with hepatitis B or active cytomegalovirus (CMV) as determined by PCR.

9. Previous exposure to a BTK or Bcl-2 inhibitor therapy within 14 days of initiating study treatment on Cycle -1 Day 1, or previous exposure to anti-cancer therapy including chemotherapy, radiotherapy, or investigational therapy, including other investigational targeted small molecule agents within 21 days of initiating study treatment on Cycle 1 Day 1.

10. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails.

11. History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 administration.

12. A known history or active autoimmue disease even if not requiring systemic immunosuppression. Subjects with known history of immune thrombocytopenic purpura or autoimmune hemolytic anemia secondary to CLL are allowed to enroll.

13. Malabsorption syndromes.

14. Irritable bowel syndrome with greater than 3 loose stools per day as a baseline.

15. Any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
    a. Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV)[see Appendix: NYHA Classifications]
    b. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, CHF, or myocardial infarction within 6 months of enrollment.
    c. Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.

d. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting within 6 months of enrollment.

16. Females who are pregnant or lactating.

4. Registration Procedures

4.1 Patient Registration

Patients will be centrally registered with the Weill Cornell Medicine (WCM), Division of Hematology and Medical Oncology, Joint Clinical Trials Office. To register a patient, email the following documents to your assigned registration contact:

- WCM Patient registration form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Fully executed HIPAA research authorization form (if separate from the consent document)
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- Redacted source documentation to verify eligibility

Central registration documents should be scanned/emailed Monday to Friday from 9:00 AM to 4:00 PM EST to study investigators and jctoiit@med.cornell.edu, along with all other assigned registration contacts for this study. Central registration information is reviewed and entered into the REDCap database by the Coordinating Center. Patients will be assigned a sequence number for the protocol. The registering institution will then be emailed a copy of the sequence number as confirmation of a completed registration. Subjects should NOT receive any study medication prior to receipt of registration confirmation. Note that attachments larger than 4.5 MB are not accepted, so larger attachments should be split into more than one email.

Registration of patients cannot occur until the Coordinating Center has received proper documentation from the registering institution of IRB approval, including a copy of the current approval letter, stamped consent and signed FDA Form 1572, along with other required regulatory documents. These documents will be requested at site activation and may be scanned/emailed to the Coordinating Center.

5. Study Procedures

5.1 Schedule of Evaluations

Table 1. Schedule of trial events

Schedule of Assessments		Year 1												
				Cycle 1										
Study Procedure	Screening	C-1 D1	C-1 D15	Day 1	Day 2	Day 8	Day 15	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C10 D1
Informed Consent	X													
Inclusion/Exclusion	X													
ECOG	X	X	X	X				X	X	X	X	X	X	X
Demographics	X													
Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X			X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X	X	X	X				X	X	X	X	X	X	X
EKG	X													
Bone Marrow Biopsy	X													
Bone Marrow Aspirate	X													
CBC with diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry (CMP)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Rapid Screen	X													
Hepatitis Antibody Screen[b]	X													
Cytomegalovirus (CMV) PCR	X									X			X	X
B-HCG[c] (FCBP only)	X													
Circulating DNA (research)		X		X				X					X	
Clonal Evolution Analysis (research)		X		X				X					X	
Ublituximab Infusion				X	X	X	X	X	X	X	X	X		
Umbralisib Dispensation		X	X	X				X	X	X	X	X	X	X
Adverse Event Monitoring[d]	At each timepoint AEs will be collected													
Radiologic Evaluation[e]	X							X					X	

Schedule of Assessments	Year 2				Year 3+	EOT	Follow-up*
Study Procedure	C13 D1	C16 D1	C19 D1	C22 D1	C25 D1 then Every 3 months	30 days post last dose	Every 3 months
Informed Consent							
Inclusion/Exclusion							
ECOG	X	X	X	X	X	X	X
Demographics							
Medical History	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Height							
Weight	X	X	X	X	X	X	X
EKG							
Bone Marrow Biopsy							
Bone Marrow Aspirate							
CBC with diff	X	X	X	X	X	X	X
Serum Chemistry (CMP)[a]	X	X	X	X	X	X	X
HIV Rapid Screen							
Hepatitis Antibody Screen[b]							
Cytomegalovirus (CMV) PCR	X	X	X	X	X		
B-HCG[c] (FCBP only)							
Circulating DNA (research)	X		X		X	X	
Clonal Evolution Analysis (research)	X		X		X	X	
Ublituximab Infusion							
Umbralisib Dispensation	X	X	X	X	X		
Adverse Event Monitoring[d]	At each timepoint AEs will be collected						
Radiologic Evaluation[e]	X		X				X (q12mo)

Footnotes:

* Subjects who discontinue treatment due to toxicity, but have not progressed will continue in study follow-up. Visits should occur q3months after EOT visit or until subsequent non-study drug administration. Patients who discontinue treatment due to progression of disease will enter survival follow-up. Survival follow-up will be documented by phone call every 6 months up to 5 years.

a. CMP includes a Basic Metabolic panel (Sodium, potassium, chloride, bicarb, blood urea nitrogen, creatinine, calcium, glucose) and a Hepatic function panel (protein total, albumin, globulin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase), Uric acid required only at screening, C-1 D1, C-1 D15, C1 D1, and C1 D2.

b. Hepatitis antibody screening will consist of Hepatitis A ab, HBsAg, HBcAb, Hepatitis C Ab. If HBcAb is positive, an HBV DNA PCR should be performed.

c. B-HCG pregnancy testing required only for females of child bearing potential (FCBP). At screening should be tested by serum within 3 days prior to C-1 D1.

d. Adverse events should be assessed up to 30 days post last dose. For all serious adverse events (SAE), concomitant medications should be assessed and appropriately captured/reported.

e. CT neck, chest, abdomen, pelvis with contrast. Radiologic evaluation during follow-up should occur every 12 months or as clinically warranted to document disease progression.

5.1.1 Screening Visit

- Informed consent
- Inclusion/exclusion checklist
- ECOG
- Medical history
- Physical exam
- Vital Signs
- Height
- Weight
- EKG
- Bone marrow biopsy
- Bone marrow aspirate
- CBC with differential
- CMP (with uric acid)
- HIV
- Hepatitis antibody screen
- CMV testing by PCR
- For women of childbearing age serum B-HCG within 3 days prior to Cycle -1 Day 1
- CT neck, chest, abdomen and pelvis with contrast

5.1.2 Treatment Phase

5.1.2.1 Cycle -1 Day 1

- ECOG
- Medical history
- Physical exam
- Vital Signs
- Weight
- CBC with differential
- CMP (with uric acid)
- Research tubes (2 purple top tubes for banking)
- Umbralisib pill dispensation
- Adverse event assessment

5.1.2.2 Cycle -1 Day 15

- ECOG
- Medical history
- Physical exam
- Vital Signs
- Weight
- CBC with differential
- CMP (with uric acid)

- Umbralisib pill dispensation
- Adverse event assessment

5.1.2.3 Cycle 1 Day 1

- ECOG
- Medical history
- Physical exam
- Vital Signs
- Weight
- CBC with differential
- CMP (with uric acid)
- Research tubes (2 purple top tubes for banking)
- Ublituximab infusion
- Umbralisib pill dispensation
- Adverse event assessment

5.1.2.4 Cycle 1 Day 2

- Medical history
- Physical exam
- Vital Signs
- Weight
- CBC with differential
- CMP (with uric acid)
- Ublituximab infusion
- Adverse event assessment

5.1.2.5 Cycle 1 Day 8 and 15 (+/- 2 days)

- ECOG
- Medical history
- Vital Signs
- Weight
- CBC with differential
- CMP
- Ublituximab infusion
- Adverse event assessment

5.1.2.6 Cycle 2-6, Day 1 (+/- 2 days)

- ECOG
- Medical history
- Physical exam

- Vital Signs
- Weight
- CBC with differential
- CMP
- Research tubes (2 purple top tubes for banking) (Cycle 2 only)
- Ublituximab infusion (+/- 3 days)
- Umbralisib pill dispensation
- CT neck, chest, abdomen and pelvis with contrast (Prior to C2D1 only +/- 7 days)
- CMV testing by PCR
- Adverse event assessment

5.1.2.7 Cycle 7, Day 1 and Beyond, Study visits occur every 3 cycles with a Day 1 visit (+/- 5 days)

- ECOG
- Medical history
- Physical exam
- Vital Signs
- Weight
- CBC with differential
- CMP
- Research tubes (2 purple top tubes for banking) (Cycle 7, 13, 19, 25 only)
- Umbralisib pill dispensation
- CT neck, chest, abdomen and pelvis with contrast (Prior to C7D1, C13D1, C19D1, C25D1only +/- 7 days)
- CT neck, chest, abdomen and pelvis C37D1, C49D1, C61D1 +/- 7 days for subjects on study beyond 2 years.
- CMV testing by PCR
- Adverse event assessment
- After Cycle 7D1 study visit and response assessments subjects must be evaluated for objective response by treating investigator. See Section 5.4.1 for further details in subject management.

5.1.2.8 End of Treatment Visit (30 days post last dose)

- ECOG
- Medical history
- Physical exam
- Vital Signs
- Weight
- CBC with differential
- CMP

- Research tubes (2 purple top tubes for banking)
- Return all study drug in subject possession.
- Adverse event assessment

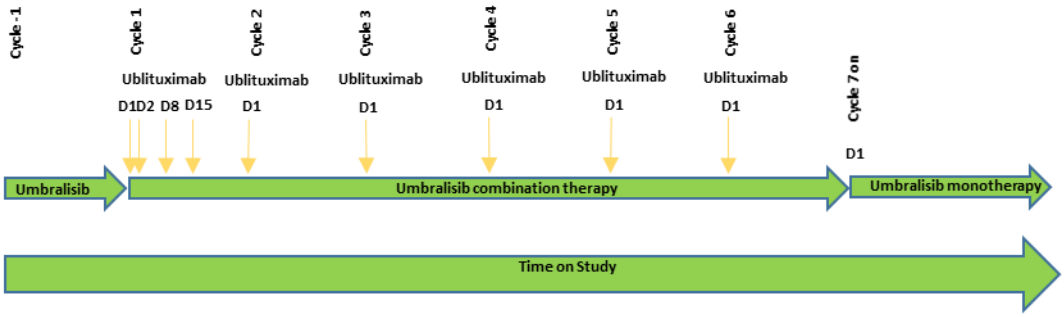
5.2. Treatment Administration

All treatment will be administered on an outpatient basis. See section 5.2.1 and 5.2.2 for special precautions relevant for each specific study agent administration. All therapy will be administered in cycles with each cycle consisting of 28 days.

Enrolled subjects will initiate umbralisib monotherapy for a one cycle lead-in defined by Cycle -1. This cycle is designed to allow for correlative assay sample collection to assess early clonal shifts after umbralisib therapy. Without the lead-in these shifts may otherwise be masked by peripheral elimination of circulating tumor cells by anti-CD20 therapy. Subjects will be monitored closely upon initiation with a C-1D15 visit to assess tolerability of umbralisib monotherapy. Upon completion of Cycle -1 subjects will then continue on daily umbralisib and initiate combination therapy with ublituximab (U2). Ublituximab administration and induction/continuation is defined in Section 5.2.1. Ublituximab will only be administered through Cycle 6 (i.e no maintenance administration). Starting at C7D1 enrolled subjects will continue on umbralisib monotherapy. Umbralisib will be given on a continuous once daily basis starting at Cycle -1 for each 28 cycle until disease progression, discontinuation due toxicity, subject death, subject withdrawal of consent, or investigator withdrawal. Administration schedule and timing of umbralisib administration in relation to ublituximab are further defined in Section 5.2.3. The overall treatment administration is depicted in the schema below Figure 1.

Subjects will be evaluated for objective response after completion of 6 cycles of combination therapy. Subjects with a response ≥ PR will be allowed to continue on study (umbralisib monotherapy maintenance). A subject that does not meet objective response criteria by IwCLL 2018 guidelines outlined in Section 9.1 at C7D1 must be taken off study. See section 5.4.1 for further details in management of these subjects not meeting strict response criteria after completion of combination therapy.

Figure 1. Study Drug Administration Schema



5.2.1 Ublituximab

Ublituximab infusions will be administered as an outpatient and consistent with previous Phase II and Phase III dosing schemes. During Cycle 1, infusions will occur on Day 1, Day 2, Day 8, and Day 15. On days 1 and 2 the 900mg will be split, with each subject receiving 150mg on day 1 and the remaining 750mg on day 2. All subsequent infusions starting from Cycle 1 Day 8 will consist of a single 900mg infusion of ublituximab. After completion of Cycle 1, dosing of ublituximab will occur on a monthly basis (q28 days) on day 1 of Cycles 2-6 (+/- 3 days). Starting at Cycle 1 Day 1 through Cycle 6 Day 1 ublituximab infusions will be in combination with oral administration of umbralisib. After 6 cycles of combination treatment, ublituximab infusions will be stopped and subjects will continue on umbralisib monotherapy. Titration schedules should follow the schema depicted in the Table 2. Upon completing Cycle 6 ublituximab infusions will be completed and subjects will not receive maintenance ublituximab. Subjects will continue with umbralisib monotherapy as described in Section 5.2.3.

Subjects will be eligible to start a new cycle of combination therapy with ublituximab unless they are experiencing toxicity requiring treatment delay as outlined in Section 6.2 Table 4.

Ublituximab should not be administered as an IV push or bolus. All subjects must be premedicated before ublituximab infusion with an antihistamine (diphenhydramine 50mg or equivalent), and a corticosteroid (dexamethasone 20 mg or equivalent dose) as follows:

- If pre-medications are administered IV: start the ublituximab infusion 30 minutes after conclusion of the last pre-medication infusion. If IV premedications are given over longer than a 30 minute timeframe per institutional standards, begin ublituximab within 10 minutes of stop time of last pre-medicaiton.
- If pre-medications are administered orally: start the ublituximab infusion 45-60 minutes after ingestion of the oral pre-medications
- 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

Corticosteroid premedication should be given on day 1, 8 and 15 of cycle 1. Subsequent use of steroid premedication starting with cycle 2, will be left to investigator discretion and is not mandatory with these subsequent infusions in the absence of infusion related reactions with previous doses. Use of oral acetaminophen 650 mg (or equivalent) should be restricted to patients who experience fever or pyrexia after week 1 dose, or as clinically warranted. During infusion the following monitoring schema should be followed by nursing:

a) Nurse should remain with the patient during the first 15 minutes of the infusion
b) Nurses should monitor vital signs (temperature, BP, and HR) and assess for signs of infusion reaction every 15 minutes for the first hour, then every 30 minutes for the remainder of the infusion, and upon infusion completion

Table 2. Ublituximab Titration Schedules

Cycle 1 Day 1 & 2 infusion of 4 hours

Cycle 1	Ublituximab Dose	Total volume to be infused	Infusion rate			
			T0 to T30min	T30min to T1H	T1H to T2H	T2H to T4H
Day 1	150 mg	250 mL	10 mL/H	20 mL/H	35 mL/H	100 mL/H
Day 2	750 mg	500 mL	10 mL/H	20 mL/H	85 mL/H	200 mL/H

Cycle 1 Day 8 & 15 infusion of 3 hours

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

Cycle 2 and remaining infusions over 90 minutes

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

5.2.2 Management of Infusion Related Reactions

Since infusion-related hypotension may occur, antihypertensive medications should be held 12-24 hours prior to and throughout ublituximab infusion. Infusion related reactions including severe reactions have been reported with ublituximab administration in patients with CLL. 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 flow rate at their discretion.

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

1st or 2nd Infusion Interruption:

- Hold infusion and closely monitor patient, institute symptomatic medical management until resolution of IRR symptoms. Treating investigator must be notified by research team and documentation should occur in the patient chart.
    - Symptomatic medical management should include administration of acetaminophen, antihistamines, and/or corticosteroids for fever (temperature >38°C) and/or chills
    - Physician may order meperidine for persistent rigors, caution to be exercised if

patient is hypotensive and meperidine may contribute to ongoing hypotension.
    - Administer antihistamines and/or corticosteroids for flushing, urticarial, pruritus, or angioedema
    - Administer IV fluid boluses for hypotension
    - Administer epinephrine, corticosteroids and antihistamines in the event of an anaphylactic reaction
- Following the judgment of the Investigator, and provided the patient is stable, the infusion may be resumed at 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 at the treatment cycle dose (see Section 5.2.1
- For any Grade 4 infusion related reaction, ublituximab should be stopped indefinitely. Subjects that experience a Grade 4 infusion reaction will not be allowed to be rechallenged.

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.
- Administer symptomatic medical management as above.
- Any remaining diluted investigational product should be discarded.
- If the infusion discontinued is the Cycle 1 Day 1 infusion, administer the scheduled Cycle 1 Day 2 dose according to the protocol dosing schedule.
- For any Grade 4 infusion related reaction ublituximab should be stopped indefinitely. Subjects that experience a Grade 4 infusion reaction will not be allowed to be rechallenged.

5.2.3 Umbralisib

Umbralisib will be administered orally as four 200mg capsules taken once daily for a total daily dose of 800mg. Umbralisib should be taken within 30 minutes of starting a meal. All subjects will initiate a one cycle lead in prior to starting combination therapy with ublituximab, subjects will initiate taking umbralisib on Cycle -1 day 1 through Cycle -1 day 28. Starting on Cycle 1 day 1, subjects may take the dose of umbralisib before or after infusion with ublituximab but umbralisib must be taken within 30 minutes of starting a meal. Subjects will continue daily oral dosing of 800mg umbralisib for 28 days which will constitute a cycle. Subjects should try to take the drug at the same time each day throughout the trial. Subjects should be instructed to swallow the tablets whole and should not chew or crush them. If a dose of umbralisib is missed, it should be taken as soon as possible on the same day. If it is missed for a period of greater than 12 hours, it should be skipped for that day. If vomiting occurs, no attempt should be made to replace the vomited dose. Subjects will continue daily dosing of umbralisib until disease progression, toxicities, or study completion whichever comes first.

Subjects will be eligible to start a new cycle of either combination or monotherapy of umbralisib unless they are experiencing toxicity requiring treatment delay as outlined in Section 6.2 Table 4.

Umbralisib will be dispensed at the sites by the research coordinator or designee under the direction of the PI or by a pharmacist at the site. Before dispensing, the site pharmacist or authorized designee 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.

Subjects must be provided drug in its original container. Subjects will be dispensed sufficient umbralisib for roughly 1 cycle of treatment. If the interval between visits is greater than 1 cycle, subjects may be given more than 1 cycle of umbralisib so that they do not have to return between scheduled visits. Subjects 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 subject at the beginning of each new treatment cycle and as needed.

5.3 General Concomitant Medication and Supportive Care Guidelines

No clinical drug drug interactions with ublituximab or umbralisib have been reported to date and thus there are no specific prohibited concomitant medications based on potential for drug drug interactions. Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted and patient should receive full supportive care during study participation (including fluids and electrolyte replacement, and antibiotics when appropriate). Use of myeloid growth factors or red blood cell growth factors (erythropoietin) is permitted per institutional policy. Transfusions may be given in accordance with institutional policy. After consultation with the Sponsor the following may be considered; localized hormonal or bone sparing treatment for non-B-cell malignancies. Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (i.e., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 60 mg per day of prednisone or equivalent are permitted. Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 60 mg per day of prednisone or equivalent, IVIG will be allowed for immune mediated platelet or red cell destruction or for hypogammaglobulinemia and infection risk. IVIG may not be given on the same day as ublituximab.

Prophylactic antibiotics against Pneumocystis jiroveci pneumonia (PJP) should start prior to starting umbralisib. All subjects should also be prophylaxed against herpes zoster virus with famciclovir, valacyclovir or acyclovir. Dapsone 100mg daily is recommended for PJP prophylaxis, but the agents of choice for antibiotic prophylaxis is left to investigator discretion. Standard dosing for prophylactic purposes should be followed for each respective required antibiotic.

Any non-study protocol related chemotherapy, anti-cancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is on protocol except as outlined above.

5.4 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s) greater than 8 weeks from scheduled dose, combination treatment may continue for 6 months followed by at least 18 months of

umbralisib monotherapy. Patients deriving benefit at 2 years will be allowed to continue on study drug. If a subject meets the following criteria, they will be removed from study treatment:

- Disease progression
- Failure to achieve ≥ PR to combination therapy (See section 5.4.1)
- Intercurrent illness that prevents further administration of both study drugs
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.4.1 Procedures for Subject Removal if Less Than PR at Completion of Combination Therapy

Subjects will be evaluated for objective response after completion of 6 cycles of combination therapy ublituximab and umbralisib (i.e. C7D1 radiographic evaluation and clinical and laboratory assessment). Subjects with a response ≥ PR will be allowed to continue onto the umbralisib monotherapy maintenance portion of the study. Subjects not meeting at least the PR response definition outlined in Section 9.1.2 at the C7D1 study visit will be removed from study with the following exception;

If a subject has stable disease, is deriving clinical benefit per investigator assessment, and for whom an approved therapy with known efficacy is not available (i.e. double refractory to BTKi or Bcl2 inhibitor) those subjects will be allowed to continue on study and proceed with umbralisib monotherapy.

All subjects will be allowed to start C7D1 and continue on study for up to 3 cycles as complete response assessment data may not be readily available to make clinical decisions and arrangement of subsequent therapy may take additional time to ensure safe transition of subjects to alternative treatments. This is to prevent abrupt removal of subjects from therapy and to allow sufficient time for data to be evaluated in an objective manner. All subjects must be assessed by the investigator for suitability to continue on umbralisib monotherapy prior to C10D1. Effort must be made by investigator to expeditiously make response assessment and arrange for alternative management at the earliest timepoint prior to C10D1. No subject meeting criteria outlined in this Section 5.4.1 will be allowed to continue on study beyond C10D1.

5.5 Duration of Follow Up

The anticipated duration of patients on study therapy will be 2 years though patients deriving benefit will be allowed to continue on study beyond two years. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event even if that period is longer than 30 days after removal.

After withdrawal from protocol treatment, all patients should be followed for AEs for 30 calendar days after their last dose of either study drug. All new AEs occurring during this period

must be recorded and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease.

Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent will be followed for progression free survival and survival every 3 months until documentation of disease progression, death or initiation of CLL directed non study treatment.

Visits for subjects with early treatment discontinuation other than disease progression, death or withdrawal of consent, will continue for 3 months after study drug discontinuation. Subjects and study team should collect the following data during this follow-up period:

- ECOG
- Medical history
- Physical exam
- Vital Signs
- Weight
- CBC with differential
- CMP
- CT neck, chest, abdomen and pelvis with contrast every 12 months or as clinically warranted to document disease progression

Subjects who discontinue therapy for any reason except withdrawal of consent will be followed for overall survival for up to 5 years. Survival follow-up will be documented by either chart review if the subject remains an active patient in the investigators clinic or by phone call every 6 months up to 5 years. If subject is not in active follow-up then a chart note should be placed within the patient chart to confirm survival status.

When the first subject enters year five of treatment or follow-up the study may be amended to address continuation of study therapy or follow-up beyond year 5.

6. Dosing Delays/Dose Modifications

6.1 Ublituximab

Dose modification of ublituximab is not permitted. Dose delays will be the primary method for managing ublituximab-related toxicities (see Table 3 below: Dose delay and modification schema for umbralisib and ublituximab). During infusion dose delays should follow the guidelines outlined in Section 5.2.2.

Supportive care should be provided and growth factor support should be applied as outlined in Section 5.3.

6.2 Umbralisib

Dose delays and modifications will be the primary method for managing umbralisib related toxicities. Ublituximab and umbralisib therapy should be held upon onset of any of the following toxicities until recovery as outlined in Table 3 below. Upon recovery of toxicities as outlined in Table 3 below, umbralisib dosing should be the initial drug restarted. Ublituximab infusions should restart at least 7 days after umbralisib dosing has resumed and there has been no recurrence of the toxicity. One exception to this rule, are any toxicities related to infusion reactions. Upon recovery of any Grade 3 or greater infusion related toxicities back to baseline of less than or equal to Grade 1, the requirement of 7 days of umbralisib dosing before ublituximab dosing can be waived in order to keep patients on schedule during the first cycle induction. During the first cycle, if there is a toxicity observed that requires holding of therapy that would cause the dosing of ublituximab to fall out of window or schedule, then that dose should be skipped, the patient should reinitiate umbralisib upon recovery and be dosed with ublituximab at the next scheduled infusion per protocol. If there is a recurrence of toxicity felt attributable to ublituximab then further ublituximab infusions may be stopped at investigator discretion.

Table 3. Hematologic Grading Scheme for subjects entering with abnormal platelets or hemoglobin.

Hematologic Grading Scheme	
Grade	Decrease in platelets[1] or hemoglobin[2] from pretreatment value
0	0-10%
1	10.01-24%
2	24.01-49%
3	49.01-74%
4	≥74.01%

1. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 109/L (20,000/μL), this will be considered Grade 4 toxicity.

2. Hemoglobin levels must be below normal levels for Grades 1 to 4. Baseline and subsequent hemoglobin determinations must be performed before any given transfusions. The use of erythropoietin will not affect grading of toxicity and use should be documented

Table 4. Dose delay and modification schema for umbralisib and ublituximab.

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 2 neutropenia	Maintain current dose and schedule of umbralisib and ublituximab (if applicable). Consider supportive care as warranted.
Grade 3 neutropenia	Maintain current dose and schedule of umbralisib and ublituximab (if applicable). Consider supportive care. If recurrence or persistent Grade 3, consider reducing umbralisib to next lower dose level at discretion of the investigator.

Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay umbralisib and ublituximab (if applicable) until Grade ≤3 and/or neutropenic fever or infection is resolved; thereafter, resume umbralisib at current dose and schedule. Consider supportive care. If delay is > 56 days despite the use of G-CSF, discontinue umbralisib and, if applicable, ublituximab. When/if restarting, restart ublituximab (if applicable) after 7 days of umbralisib dosing. If recurrence after rechallenge, repeat these steps with allowance for reducing umbralisib to next lower dose level at discretion of the investigator.
	If the absolute neutrophil count was <1 x 10^9/L before therapy, the patient will not be evaluable for toxicity referable to ANC. The use of growth factors such as granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity, but should be documented. If a subject enters with a decreased ANC then any count <500 should be considered as Grade 4 and managed as outlined above.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose level and schedule of umbralisib and ublituximab (if applicable). Provide supportive care as clinically warranted.
Grade ≥3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia without bleeding	Delay umbralisib and ublituximab (if applicable) until Grade ≤3 without bleeding; thereafter, resume umbralisib at current dose and schedule. Consider supportive care intervention as warranted. If delay is > 56 days, discontinue umbralisib and, if applicable, ublituximab. Restart ublituximab (if applicable) after 7 days of umbralisib dosing. If recurrence after rechallenge, repeat these steps with allowance for reducing umbralisib to next lower dose level at discretion of the investigator.
Immune Related Pneumonitis*	
Grade 1 & 2	Stop all therapy and hold until complete resolution. Restart umbralisib at one lower dose level. Restart ublituximab (if applicable after 7 days of umbralisib dosing). If delay is > 56 days, discontinue umbralisib and, if applicable, ublituximab. If recurrence after re-challenge, discontinue all treatment therapy.
Grade ≥3	Discontinue all therapy
*** For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at investigator's discretion. While pneumonitis has been**	

minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-herpetic viral prophylaxis is required.	
Diarrhea and/or Colitis	
Diarrhea Grade ≤2	Maintain current dose and schedule if tolerable or hold umbralisib and ublituximab (if applicable); thereafter, resume umbralisib at current dose and schedule, and resume ublituximab (if applicable) after 7 days of umbralisib dosing. **NOTE**: If persistent grade 2 diarrhea, despite supportive care, delay umbralisib and ublituximab (if applicable) until ≤ grade 1; thereafter, resume umbralisib at current dose and schedule, and resume ublituximab (if applicable) after 7 days of umbralisib dosing. If recurrence after rechallenge, repeat these steps with allowance for resuming umbralisib at current dose or next lower dose level at discretion of the investigator. If delay is > 56 days, discontinue umbralisib and, if applicable, ublituximab. Restart ublituximab (if applicable) after 7 days of umbralisib dosing.
Diarrhea Grade 3	Withhold umbralisib and ublituximab (if applicable) until Grade ≤2. Resume umbralisib at next lower dose level. If delay is > 56 days, discontinue umbralisib and, if applicable, ublituximab. Restart ublituximab (if applicable) at full dose after 7 days of umbralisib dosing. If recurrence after rechallenge, repeat these steps with allowance for resuming umbralisib at next lower dose level at discretion of the investigator. A diagnostic workup for Grade 3 diarrhea should be performed including a colonoscopy to evaluate for underlying colitis. Monitoring of the patient should occur at least weekly until improvement and or resolution.
Diarrhea Grade 4	Discontinue all treatment, rechallenge prohibited.
Colitis Grade ≤ 3	Hold umbralisib and ublituximab (if applicable). Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level. If delay is > 56 days, discontinue umbralisib and, if applicable, ublituximab. Restart ublituximab (if applicable) after 7 days of umbralisib dosing.
Colitis Grade 4	Discontinue all treatment, rechallenge prohibited.
Liver Toxicity (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Grade 1	Maintain current umbralisib dose.

	Assess concomitant medications and risk factors*. Monitor labs every 1-2 weeks. Maintain full dose and schedule of ublituximab, if applicable.
Grade 2	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Begin supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent per investigator discretion) **. Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off. 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 after 7 days of umbralisib dosing. o Taper prednisone by 10 mg per week until off. If umbralisib is delayed for > 56 days, discontinue umbralisib. If ublituximab is delayed for > 56 days, discontinue ublituximab. Restart ublituximab (if applicable) after 7 days of umbralisib dosing.
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 after 7 days of umbralisib dosing. If umbralisib is delayed for > 56 days, discontinue umbralisib.

	If ublituximab is delayed for > 56 days, discontinue ublituximab. Restart ublituximab (if applicable) after 7 days of umbralisib dosing.
Grade 4	Discontinue all treatment, rechallenge prohibited.

* Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc.

**Supportive Care – Aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc.

Important: Before initiating steroids, check for viral hepatitis or CMV infection.

All Other Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level.
Grade ≥3	Withhold umbralisib and ublituximab (if applicable) until Grade ≤2; thereafter, resume umbralisib at current dose. If delay is > 56 days, discontinue umbralisib and, if applicable, ublituximab. Restart ublituximab (if applicable) at full dose after 7 days of umbralisib dosing. If recurrence after re-challenge, repeat these steps with allowance for resuming umbralisib at current dose or next lower dose level at discretion of the investigator.

STUDY DRUG DOSE REDUCTION RECOMMENDATIONS

Study Drug	**Starting Dose**	**1st Dose Reduction**	**2nd Dose Reduction**
TGR-1202	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 and after discussion with the monitor.

7. Pharmaceutical Information

7.1 Investigational Agent – Ublituximab

Ublituximab is available as a sterile, clear to opalescent, preservative-free concentrate for solution for intravenous (IV) by infusion administration. It will be supplied at a concentration of 25 mg/mL in 6 mL (150 mg) single-use glass vials. The shelf life of ublituximab is 36 months if stored between +2°C / + 8°C based on stability data and should be stored in a secured, limited-access, refrigerated area at a temperature ranging from +2°C / + 8°C. Ublituximab must not be frozen. Ublituximab must not be mixed with other medicinal products during preparation and should only be diluted with 0.9% NaCl before use.

No incompatibility of ublituximab with PVC bags containing 0.9% NaCl or PVC tubing has been observed. Studies performed in both static and dynamic conditions, showed no significant loss of CD16 activity and no adsorption or degradation of the protein were noted. Ublituximab diluted in 0.9% NaCl is stable for 24 hours in static condition at 25°C and in dynamic conditions it is stable for 8 hours at 25°C.

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.

It is recommended that ublituximab be administered immediately after dilution. It should NOT be mixed the day before and mixing should only occur once confirmed that patient is eligible for therapy on the day of treatment.

No live vaccines can be administered within 4 weeks of the initial dose of ublituximab or while receiving ublituximab.

7.2 Investigational Agent – Umbralisib

Umbralisib is available as tablets with the following description: 200 mg: Light green, oval tablets with “L474” debossed on one side and plain on the other side.

Umbralisib should be stored at temperatures between 20°C and 25°C (excursions permitted between 15°C and 30°C). Do not freeze. Based on the results available to date, a shelf life of 36 months is proposed for the drug product in the current packaging. Retest dates will be provided periodically by TG Therapeutics, Inc.

7.3 Availability

Ublituximab and umbralisib are investigational agents supplied to investigators by TG Therapeutics Incorporated (TGTX).

7.4 Investigational Agent Ordering

Ublituximab and umbralisib are available from TG Therapeutics. 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 study drug(s)
- Date needed
- Principal Investigator name
- Study title
- TG Therapeutics, Inc. tracking number (U2-NTG-004)
- Investigational drug pharmacy shipping address

7.5 Investigational Agent Accountability

Ublituximab and Umbralisib Inventory Records – The investigator, or a responsible party designated by the investigator, in this case the investigational pharmacy of Weill Cornell, will maintain a careful record of the inventory and disposition of all agents received from TGTX on a Drug Accountability Record Form (DARF). If there is any abnormality in the supplied boxes (ublituximab) or bottles (umbralisib), this should be documented during the acknowledgement of receipt and TG Therapeutics should be contacted at productquality@tgtxinc.com.

8. Correlative/Special Studies

Specific correlative studies are not planned with this protocol. However, specimens from subjects will be collected at prespecified time points as outlined in Section 5.1. These specimens will be processed and banked for potential use in future assays. Specimens will be processed and isolated for plasma and mononuclear layer buffy coats for later B and or T cell selection. Genetic analyses may be performed on isolated components. Any and all correlative analyses, including from specimens stored for future research, require written approval by TG Therapeutics, Inc. prior to initiation of the correlative analyses. Investigators and institution may not provide samples taken from subjects to anyone outside of their institution for any purpose without written pre-approval by TG Therapeutics, Inc.

9. Measurement of Effect

9.1. Response Criteria

All response criteria will be assessed using the International Workshop on CLL 2018 guidelines.

9.1.1 Complete Response

Requires all of the following:

1) Absence of clonal lymphocytes in the peripheral blood.
2) Absence of significant lymphadenopathy. (eg, lymph nodes > 1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.
3) No hepatomegaly or splenomegaly by physical examination. In clinical trials, a

CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.

4) Absence of constitutional symptoms.
5) Blood counts above the following values.
    i) Polymorphonuclear leukocytes 1.5 × 109/L (1500/μL) or more.
    ii) Platelets more than 100 × 109/L (100 000/μL).
    iii) Hemoglobin more than 110 g/L (11.0 g/dL; untransfused).

9.1.2 Partial Response

To define a partial remission, at least 2 parameters of group A and 1 parameter of group B need to improve, if previously abnormal (Table 4; sections 5.2.1 to 5.2.5). If only 1 parameter of both groups A and B was abnormal before therapy, only 1 needs to improve.

Group A

1) A decrease in the number of blood lymphocytes by less than 50% or more from the value before therapy.
2) A reduction of lymphadenopathy assessed by CT scans and must be decreased by 50% or more in the sum of products of up to 6 lymph nodes.
    i) There must be no increase in any lymph node and no new enlarged lymph nodes. In small lymph nodes <2cm an increase up to 25% is considered insignificant.
3) A decrease in the size of the liver and/or spleen by 50% or more as defined by CT scan

Group B

4) The blood count must demonstrate one of the following:
    i) Polymorphonuclear leukocytes 1.5 × 109/L (1500/μL) or more or show a 50% or greater improvement over baseline without the aid of growth factors.
    ii) Platelets more than 100 × 109/L (100 000/μL) or 50% or greater improvement over baseline
    iii) Hemoglobin more than 110 g/L (11.0 g/dL; untransfused) or 50% or greater improvement over baseline untransfused.

9.1.3 Progressive Disease

Progressive disease is characterized by at least one of the following:

1) Appearance of any new lesion such as an enlarged lymph node >1.5cm, splenomegaly, hepatomegaly, or other organ infiltrate.
2) An increase by 50% or more in the greatest determined diameter of any previous site.

3) An increase of 50% or more in the sum of the product of diameters of multiple nodes.
4) An increase in the liver or spleen by 50% or more de novo appearance of hepatomegaly or splenomegaly.
5) An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
    i) During umbralisib therapy a lymphocytosis may be seen. any lymphocytosis that occurs in the setting without establishing a nadir or in during a concurrent illness will not be counted as a progression
6) Transformation to a more aggressive histology
7) Occurrence of cytopenia attributable to CLL. During therapy cytopenias cannot be used to define disease progression.

9.1.4 Stable Disease

Any subject who has not achieved a CR or a PR and do not demonstrate progressive disease, will be considered to have stable disease.

9.2. Duration of response

Duration of response is defined as the interval between the first objective response to the first of disease progression

9.3. Progression-Free Survival

Progression-free survival is defined as the interval between the first treatment day to the first sign of disease progression or death.

9.4. Overall Survival

Overall survival duration is defined as the interval between the first treatment day to death.

10. Data Reporting / Regulatory Considerations

10.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients. REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-

based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

10.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. TG Therapeutics will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

11. Statistical Considerations

11.1 Study Design/Endpoints

In this single center Phase II study we will evaluate the efficacy and safety of umbralisib and ublituximab (U2) as salvage in patients with CLL who have progressed either on a BTK inhibitor or BCL-2 inhibitor. The study will enroll in two parallel cohorts and subjects will be assigned to cohorts based on the previous novel agent containing regimen regardless of how the novel agents were sequenced, **Cohort A** will consist of patients who progress on BTKi containing regimens and **Cohort B** will consist of patients who progress on BCL-2 containing regimens. Subjects who progress on a regimen containing both a BTKi and a BCL-2 inhibitor, will be enrolled in cohort B. Each cohort will be evaluated independently of each other.

Currently available retrospective evidence demonstrates an ORR of ~35-40% when idelalisib is used as first salvage after ibrutinib failure [11]. Given umbralisib's unique molecular properties and combination therapy with ublituximab, we hypothesize a response rate of 55% using U2 as first salvage. Salvage rates with novel agents after venetoclax failure in subjects considered double refractory are unknown. We anticipate close to 90% of patients enrolled in cohort B will have double refractory disease and represent a high risk group. Given these limitations, we anticipate a response rate of 40% in this group based off the efficacy seen with idelalisib after ibrutinib failure.

Because this is a pilot study, no formal sample size/power calculation is required. Given the anticipated different patient populations in each cohort, no cross cohort comparisons will be performed.

11.2 Analysis of Endpoints

11.2.1 Analysis of Primary Endpoints

With 12 patients enrolled in cohort A, an exact binomial (Clopper-Pearson) 95% confidence interval for the overall response rate can be constructed to have a width of approximately 57.6% (25.0%, 82.5%). This calculation assumes that the overall response rate will approach 55% in cohort A.

Similarly, with 12 patients enrolled in cohort B, an exact binomial (Clopper-Pearson) 95% confidence interval for the overall response rate can be constructed to have a width of approximately 56.9% (14.1%, 70.9%). This calculation assumes that the overall response rate will

approach 40% in cohort B.

11.2.2 Analysis of Secondary and Exploratory Endpoints

Analysis of outcomes will remain descriptive. With 12 patients enrolled in Cohort A, an exact binomial (Clopper-Pearson) 95% confidence interval for the CR rate can be constructed to have a width of approximately 46.3% (2.1%, 48.4%). This calculation assumes that the CR rate will approach 16.7% in cohort A. Similarly with 12 patients enrolled in cohort B, and exact binomial (Clopper-Pearson) 95% confidence interval for the CR rate can be constructed to have a width of approximately 38.5% (0.2%, 38.5%) This calculation assumes the CR rate will approach 8% in cohort B. Assuming adequate follow-up time, Kaplan-Meier survival analysis will be used to assess DoR.,PFS, and OS, in the entire cohort. All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for median DoR/PFS/OS-time and DoR/PFS/OS proportions, will be calculated to assess the precision of the obtained estimates. Safety will be collected and adverse events will be tabulated per incidence of specific AE terms will be reported for the entire cohort. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and Stata Version 15.0 (StataCorp, College Station, TX).

11.3 Interim Analysis

As this is a single center pilot study with low enrollment numbers no interim analysis will be performed.

11.4 Reporting and Exclusions

11.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with ublituximab or umbralisib. If a subject comes off study due to an adverse event, the subject will be followed for 30 days or until resolution of the toxicity to baseline grade, whichever is longer.

11.4.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have completed at least one cycle of ublituximab and umbralisib combination therapy.

12. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, radiographic imaging, and physical exam.

12.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

12.1.1 Ublituximab Risks

The following adverse events were observed in patients treated with single agent ublituximab and were considered at least possibly related to ublituximab. The preliminary safety data as of May 1, 2018 is provided for a total of 117 subjects exposed to single agent ublituximab with a maximum follow up of 2+ years. See the latest ublituximab investigator brochure for a complete list of all adverse events reported regardless of causality.

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** neutropenia, thrombocytopenia
- **General Disorders and Administration Site Conditions:** pyrexia
- **Injury, Poisoning and Procedural Complications:** infusion related reaction
- **Nervous System Disorders:** headache

Common (≥ 2 - < 10%)

- **Blood and Lymphatic System Disorders:** anemia, pancytopenia
- **Gastrointestinal Disorders:** diarrhea, abdominal pain, nausea, oral pruritus
- **General Disorders and Administration Site Conditions:** fatigue, asthenia, chills, edema peripheral, pain
- **Hepatobiliary Disorders:** cytolytic hepatitis
- **Infections and Infestations:** herpes zoster
- **Investigations:** aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased
- **Musculoskeletal and Connective Tissue Disorders:** muscular weakness
- **Nervous System Disorders:** dysgeusia
- **Respiratory, Thoracic and Mediastinal Disorders:** throat irritation, throat tightness
- **Skin and Subcutaneous Tissue Disorders:** pruritus, hyperhidrosis
- **Vascular Disorders:** hypertension

12.1.2 Umbralisib Risks

The following adverse events were observed in patients treated with single agent umbralisib and were considered at least possibly related to the study medication, umbralisib. The preliminary safety data as of May 1, 2018 is provided for a total of 136 subjects exposed to single agent

umbralisib with a maximum follow up of 5+ years. See the latest umbralisib investigator brochure for a complete list of all adverse events reported regardless of causality.

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** neutropenia
- **Gastrointestinal Disorders:** nausea, diarrhea, vomiting
- **General Disorders and Administration Site Conditions:** fatigue

Common (≥ 2% - < 10%)

- **Blood and Lymphatic System Disorders:** anemia, thrombocytopenia, leukocytosis, lymphocytosis
- **Ear and Labyrinth Disorders:** tinnitus
- **Eye Disorders:** vision blurred
- **Gastrointestinal Disorders:** constipation, abdominal pain, abdominal distension, dyspepsia, colitis, dry mouth
- **General Disorders and Administration Site Conditions:** pyrexia, edema peripheral
- **Infections and Infestations:** pneumonia, oral candidiasis
- **Injury, Poisoning and Procedural Complications:** contusion
- **Investigations:** weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
- **Metabolism and Nutrition Disorders:** decreased appetite, dehydration, hyperglycaemia, hypokalaemia, hypophosphataemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, pain in extremity
- **Nervous System Disorders:** dizziness, headache, dysgeusia, tremor
- **Psychiatric Disorders:** insomnia
- **Respiratory, Thoracic and Mediastinal Disorders:** cough
- **Skin and Subcutaneous Tissue Disorders:** rash maculo-papular, alopecia, night sweats, pruritus, rash

12.1.3 Ublituximab + Umbralisib Combination Risks

Adverse Events and Potential Risks

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

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** anemia, neutropenia
- **Gastrointestinal Disorders:** diarrhea, nausea, vomiting
- **General Disorders and Administration Site Conditions:** fatigue

- **Injury, Poisoning and Procedural Complications:** infusion related reaction
- **Metabolism and Nutrition Disorders:** decreased appetite

Common (≥1% - < 10%)

- **Blood and Lymphatic System Disorders:** thrombocytopenia
- **Cardiac Disorders:** cardiac failure congestive
- **Ear and Labyrinth Disorders:** ear congestion, ear discomfort
- **Eye Disorders:** conjunctival pallor, conjunctivitis, corneal edema, vision blurred
- **Gastrointestinal Disorders:** abdominal discomfort, abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastroesophageal reflux disease, hematochezia, salivary hypersecretion, stomatitis
- **General Disorders and Administration Site Conditions:** asthenia, chills, face edema, infusion site pain, local swelling, edema peripheral, pyrexia, systemic inflammatory response syndrome
- **Hepatobiliary Disorders:** hyperbilirubinaemia
- **Immune System Disorders:** hypogammaglobulinaemia
- **Infections and Infestations:** bronchitis, cellulitis, clostridium difficile colitis, enterocolitis infectious, oral candidiasis, oral herpes, otitis media, pneumonia, pneumonia streptococcal, rhinovirus infection, sepsis, sepsis syndrome, sinusitis, skin infection, upper respiratory tract infection, urinary tract infection
- **Injury, Poisoning and Procedural Complications:** wound
- **Investigations:** alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, computerized tomogram thorax abnormal, immunoglobulins decreased, weight decreased
- **Metabolism and Nutrition Disorders:** dehydration, failure to thrive, hyperglycaemia, hyperuricaemia, hypokalaemia, hypophosphataemia
- **Musculoskeletal and Connective Tissue Disorders:** joint swelling, muscle spasms, muscular weakness, myalgia, pain in extremity
- **Nervous System Disorders:** dizziness, dysgeusia, headache, lethargy, sinus headache, somnolence
- **Psychiatric Disorders:** agitation, anxiety
- **Renal and Urinary Disorders:** micturition urgency, renal failure, renal failure acute
- **Reproductive System and Breast Disorders:** scrotal cyst, semen discoloration
- **Respiratory, Thoracic and Mediastinal Disorders:** choking, cough, dysphonia, dyspnea, epistaxis, hypoxia, oropharyngeal pain, pneumonitis, productive cough, sinus congestion
- **Skin and Subcutaneous Tissue Disorders:** alopecia, cold sweat, dermatitis acneiform, dermatitis bullous, dry skin, ecchymosis, pruritus, rash, maculo-papular, rosacea, urticaria
- **Vascular Disorders:** hypertension

12.2 Adverse Event Characteristics and Related Attributions

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

12.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart.

12.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
https://research.weill.cornell.edu/sites/default/files/immediate_reporting_policy.pdf

12.5 Definition of SAE

SAE's include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Planned hospitalizations are an exception and events due to progression that lead to hospitalization will not be considered SAEs. For all SAEs, concomitant medications should be assessed, captured, and appropriately reported with the SAE report.

12.6 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
https://research.weill.cornell.edu/sites/default/files/immediate_reporting_policy.pdf

12.7 Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. The investigator must notify the FDA of any SAE's as soon as possible but no later than 7 calendar days after the initial receipt of the information

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room

5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

12.8 Reporting of SAE to TG Therapeutics

Institution will send TG Therapeutics copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial. SAEs require expeditious handling and reporting to TG Therapeutics in order to comply with regulatory requirements. All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to TG Therapeutics at safety@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).

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

During the course of the study, all female patients of childbearing potential must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator). The definition of "females NOT of childbearing potential" is in Appendix - Contraception Guidelines and Pregnancy.

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 and the investigator must submit a Pregnancy Report Form to TG Therapeutics at safety@tgtxinc.com within 24 hours of the first knowledge of the event by the treating physician or research personnel.

Abortions (spontaneous, accidental, or therapeutic) must also be reported to TG Therapeutics at safety@tgtxinc.com using a Pregnancy Report Form within 24 hours of awareness.

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.

In the event a subject's partner becomes pregnant, a Pregnancy Report Form should be completed and submitted to TG Therapeutics, Inc. at safety@tgtxinc.com, 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.

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

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 at safety@tgtxinc.com 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.

12.9 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

13. Data and Safety Monitoring Plan (DSMP)

Monitoring activities will be commensurate with the nature, size and complexity of the trial in accordance with institutional policies and will be determined after IRB and Data Safety Monitoring Committee (DSMC) review of the protocol immediately prior to study activation. For this study we will utilize a Weill Cornell Medicine DSMC.

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APPENDIX A: 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 4 months after the last dose of study treatment. Effective contraception is defined as either:

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

The following are <u>unacceptable</u> 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 4 months after the last dose of either 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 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 5 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.

APPENDIX B: NEW YORK HEART ASSOCIATION CLASSIFICATION

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.