DF/HCC Protocol #: 19-011

TITLE: A Phase 2 Study of Umbralisib and Rituximab as Initial Therapy for Patients with Follicular Lymphoma and Marginal Zone Lymphoma

Coordinating Center: Massachusetts General Hospital Cancer Center
55 Fruit Street
Boston MA 02114

Principal Investigator (PI): Jacob D. Soumerai, MD
Center for Lymphoma, MGH Cancer Center
55 Fruit Street
Boston MA 02114
Telephone – 617-724-4000
Fax – 617-643-1915
jsoumerai@mgh.harvard.edu

Other Investigators: Jon Arnason, MD
Beth Israel Deaconess Medical Center
jarnason@bidmc.harvard.edu

Statistician:
Robert Redd, MS
DF/HCC Biostatistics Core
rredd@jimmy.harvard.edu

Study Coordinator:
Grace McCambridge
MGH Cancer Center
gmccambridge@mgh.harvard.edu

Responsible Research Nurse:
Rosalba Martignetti, RN
MGH Cancer Center
RMARTIGNETTI@PARTNERS.ORG

Responsible Data Manager:
Elizabeth Simkins, MPH
MGH Cancer Center
esimkins@mgh.harvard.edu

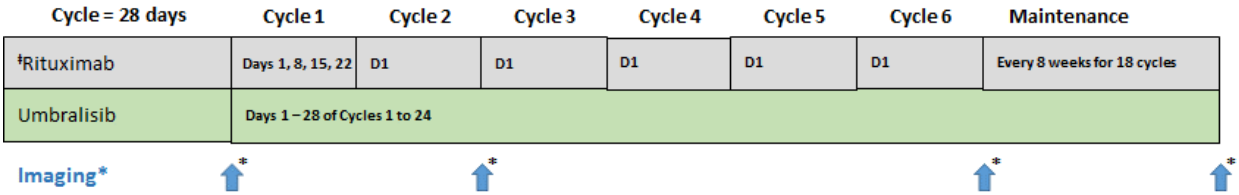
Other Agent(s): Umbralisib (TG Therapeutics), Rituximab (Commercial)

IND #: 143102
IND Sponsor: Jacob Soumerai, MD

This trial is supported by TG Therapeutics, Inc. (Tracking Number: TGR-NTG-005)

Protocol Version Date: 30/May/2024

SCHEMA



* Imaging for response evaluation to be performed at baseline, after cycle 2, after cycle 6; then every 6 months during umbralisib maintenance therapy; then every 12 months during post-treatment surveillance.

ǂ If the day 1 infusion cannot be completed within 1 day, the remainder may be infused the following day on day 2. Rituximab Cycle 1 Day 1/8/15/22 to be received by intravenous infusion; subsequent rituximab may be administered by intravenous infusion (See Section 7.2) or by subcutaneous injection (See Section 7.3).

UPDATE: 30/MAY/2024:
All patients have discontinued protocol therapy, and further data will NOT be collected on study. As such, all patients are to be prematurely withdrawn from the study.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a phase 2 single arm study of umbralisib and rituximab in patients with previously untreated follicular lymphoma and marginal zone lymphoma. Umbralisib will be administered at 800 mg by mouth daily on days 1-28 of cycles 1-24. Rituximab will be administered at 375 mg/m^2 weekly on days 1, 8, 15, 22 of cycle 1, on day 1 of cycles 2 to 6, then every 8 weeks until completion of 24 cycles of umbralisib. The primary objective is to determine the complete response rate of umbralisib and rituximab, and patients undergo response evaluation after cycle 2, after cycle 6, then every 6 months until progression.

1.2 Primary Objectives

1.2.1 To determine the complete response rate of umbralisib and rituximab in previously untreated patients with follicular lymphoma grade 1-3a and marginal zone lymphoma

1.3 Secondary Objectives

1.3.1 To assess safety and tolerability measured by the nature, frequency, severity, and timing of adverse events
1.3.2 To determine the frequency of complete plus partial responses (overall response rate)
1.3.3 To determine the durability of clinical benefit as measured by progression-free and overall survival

1.4 Correlative Objectives

1.4.1 To evaluate for mechanisms of resistance to PI3Kδ inhibition in patients with follicular lymphoma

2. BACKGROUND

2.1 Study Disease(s)

Indolent B-cell lymphomas account for a large proportion of the 70,000 new cases of non-Hodgkin lymphoma (NHL) diagnosed every year in the US, and approximately 20% of these represent follicular lymphoma (FL). While FL is a highly treatable disease, it is characterized by marked disease heterogeneity and is incurable with standard therapies.

Clinical trials of early initiation of chemotherapy in asymptomatic non-bulky patients have shown no survival benefit compared to active surveillance with initiation of treatment when indications arise, so initial observation is the standard of care for non-bulky asymptomatic patients. Indications for therapy include bulky or rapidly growing disease, symptomatic disease, disease impairing organ or marrow function, or transformation.

Patients with low disease burden in need of therapy may be treated with rituximab monotherapy with or without rituximab maintenance. Several maintenance strategies have been studied following rituximab monotherapy, and have been associated with improved PFS without an OS benefit.

Regimen	OR	CR	PFS	OS
Rituximab	70.8 – 74%	16.9 – 36%	Median 23.5 months	NR

Patients with high disease burden are typically treated with rituximab plus chemotherapy (e.g. bendamustine, CHOP, or CVP). No OS benefit has been demonstrated in trials comparing BR and R-CHOP/R-CVP (STIL and BRIGHT Trials). Therefore, choice of therapy has been based upon balancing efficacy and tolerability.

Regimen	OR	CR	5-year PFS	5-year OS
BR	92.7 – 97.0%	31 – 39.6%	50 – 65.5%	80.1 – 81.6%
R-CHOP/R-CVP	91 – 91.3%	25 – 30%	30 – 55.8%	77.8 – 85%

R-CHOP, R-CVP and BR are associated with frequent hematologic and non-hematologic toxicities. There remains an ongoing need to develop novel chemotherapy-sparing strategies for the initial treatment of FL.

The first-in-class PI3Kδ inhibitor idelalisib is highly active in patients with multiply relapsed or refractory FL with an overall response rate (ORR) of 54% in a treatment-refractory population of patients with relapsed/refractory disease despite prior CD20 antibody and alkylator therapy, but its immunomodulatory effects and associated immune-mediated toxicities have limited its development in the upfront setting.[11] The 2nd generation pan-class I PI3Kδ inhibitor copanlisib is also approved for patients with multiply relapsed or refractory FL but requires intravenous administration every 2 weeks.[12]

Umbralisib is an orally bioavailable 2nd generation PI3Kδ inhibitor with a distinct molecular structure and appears highly active in previously treated patients with FL.[1] Umbralisib is distinguished from other agents in its class by its favorable toxicity profile and infrequent immune-mediated toxicities. In Umbralisib is therefore an optimal agent for evaluation in the upfront setting, and we propose this phase 2 study of umbralisib and rituximab in previously untreated patients with follicular lymphoma grade 1-3a.

2.2 Umbralisib

Umbralisib is a highly-specific and orally available inhibitor of phosphoinositide-3-kinase (PI3K) delta (δ) and casein kinase-1 epsilon (CK1ε) with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The PI3Ks are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta isoform of PI3K is highly

expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies.

2.2.1 Preclinical Evaluations of Umbralisib

The potency of umbralisib against the human and mouse δ isoform of PI3K was evaluated in a homogeneous time resolved fluorescence (HTRF) based enzyme assay in the presence of ATP at its Km value (100 μM) (Umbralisib Investigator Brochure). Selectivity over the other three isoforms, namely, α, β, and γ was also determined (Prasanna R, 2011; Seeta N, 2011a, 2011b).

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

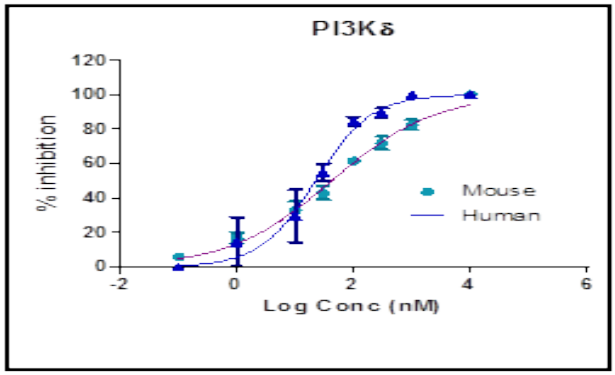


FIGURE 1: UMBRALISIB POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

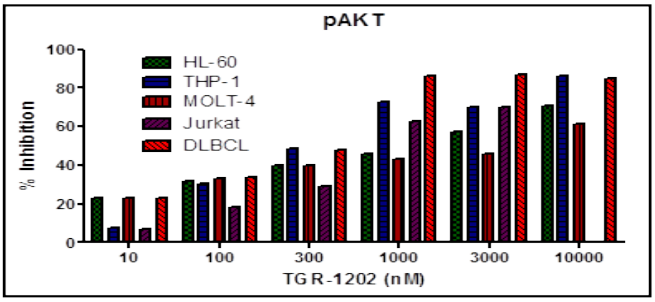
PI3K isoforms (Human)	IC50 (nM)
A	>10,000
B	1,116
Γ	1,065
Δ	22.23

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

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

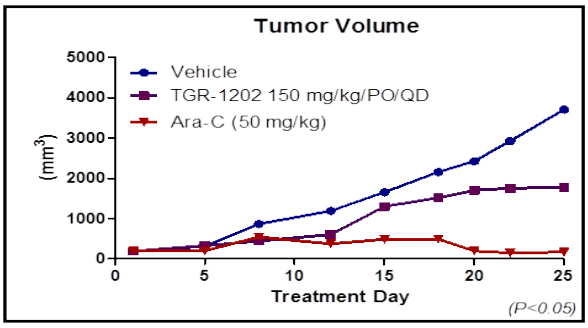
Subsequent to cell viability, the effect of umbralisib on AKT phosphorylation (Umbralisib Investigator Brochure) was determined. AKT, a serine threonine kinase mediates the downstream effects of PI3K activity and modulates several cell processes including survival and growth. Reduction of phosphorylated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

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



In vivo efficacy of umbralisib was confirmed in a subcutaneous mouse MOLT-4 xenograft model. Oral administration of 150 mg/kg/QD over a 25-day period resulted in a significant delay in tumor growth.

FIGURE 3: UMBRALISIB IN VIVO EFFICACY



2.2.2 Toxicology

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

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

Once daily oral administration by capsule of umbralisib was well tolerated in dogs at levels of 50 and 150 mg/kg/day. The gastrointestinal tract, based on clinical signs, was the target organ system. Based on effects on body weight and the incidence and severity of emesis and diarrhea, the NOAEL was considered to be 150 mg/kg/day (114.5 mg/kg/day as free base) in this species. Refer to the Umbralisib Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

2.2.3 CLINICAL DEVELOPMENT OF UMBRALISIB

2.2.3.1 Single-Agent in Patients with Relapsed or Refractory Hematologic Malignancies

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

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

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

Among 73 subjects in the modified intention-to-treat population, which included subjects who received at least 800 mg per day of the original formulation or any dose of the micronized formulation and had at least one response assessment, 53 (73%) had reductions in disease burden, including 33 (45%) subjects with reductions of 50% or more, of which three (4%) were a complete response and 30 (41%) were a partial response. In subjects with relapsed or refractory CLL, 17 (85%) of 20 achieved an objective response, with ten (50%) achieving an objective response per 2008 IWCLL criteria, seven (35%) achieving a partial response with lymphocytosis, and the remaining three (15%) achieving stable disease. Of eight assessable subjects with CLL who had high-risk cytogenetic features, six (75%) had a response, of whom two (25%) had a partial response with lymphocytosis, and the remainder had stable disease. In

subjects with follicular lymphoma, nine (53%) of 17 subjects achieved an objective response, including two (12%) who achieved a complete response; the remainder had a partial response. In subjects with diffuse large B-cell lymphoma, four (31%) of 13 achieved an objective response and two (15%) further subjects achieved stable disease. Responses for the other subject subgroups were Hodgkin lymphoma: one complete response, four stable disease, four progressive disease; marginal zone lymphoma: one partial response, four stable disease; Waldenström's macroglobulinemia: two stable disease; and mantle cell lymphoma: one partial response, four stable disease, and one progressive disease. In a post-hoc exploratory analysis, tumor reductions in most subjects with indolent lymphoma and CLL treated with umbralisib tended to improve over time. The mean duration of response was 13.4 months (95% CI 7.7–19.1) in 16 subjects in the CLL cohort, 6.4 months (4.5–17.3) in four subjects in the DLBCL cohort, and 9.3 months (3.6–15.1) in nine subjects in the follicular lymphoma cohort. In a post-hoc exploratory analysis of progression-free survival, median progression-free survival was 24.0 months (95% CI 7.4 months–not reached) in 20 subjects with CLL, and 16 months (9.2 months–not reached) in 24 subjects with indolent non-Hodgkin lymphoma (follicular lymphoma, Waldenström's macroglobulinemia, and marginal zone lymphoma). Overall, umbralisib was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts. Umbralisib monotherapy is being studied in a registration directed trial in various NHL subtypes (Study UTX-TGR-205 [UNITY-NHL]; NCT02793583).

2.3 Combination umbralisib plus CD20 antibody

Phase 1b and phase 3 studies have explored combinations of umbralisib plus CD20 monoclonal antibodies in CLL/SLL and NHL (Umbralisib IB). Completed phase 1b studies of umbralisib-obinutuzumab and of umbralisib-ublituximab in relapsed/refractory CLL/SLL and NHL (TGR-GA-106; UTX-TGR-103) have confirmed that umbralisib can be safely administered at the recommended phase 2 single agent dose in combination with a CD20 antibody. In both studies, there were no unexpected toxicities, and the frequency of adverse events was consistent with the individual agents.

2.4 Rationale

There remains an ongoing need to develop novel chemotherapy-sparing strategies for the initial treatment of FL. PI3Kδ inhibitors are highly active in patients with follicular lymphoma, with the first-in-class PI3Kδ inhibitor idelalisib and the 2nd generation pan-class I PI3Kδ inhibitor copanlisib both FDA approved for patients with multiply relapsed or refractory FL.[11,12] The immunomodulatory effects and associated immune-mediated toxicities associated with idelalisib have limited its development in the upfront setting, and the need for frequent intravenous administration has limited the development of copanlisib. Umbralisib is an orally bioavailable 2nd generation PI3Kδ inhibitor with a distinct molecular structure and appears highly active in previously treated patients with FL.[1] Umbralisib is distinguished from other agents in its class by its favorable toxicity profile and infrequent immune-mediated toxicities. In Umbralisib is therefore an optimal agent for evaluation in the upfront setting, and we propose this phase 2 study of umbralisib and rituximab in previously untreated patients with follicular lymphoma grade 1-3a.

2.5 Correlative Studies Background

PI3Kδ inhibitors are highly active in patients with FL, but most patients will ultimately progress despite ongoing PI3Kδ inhibition. The mechanisms of resistance to PI3Kδ inhibition in patients with FL is poorly understood. We will therefore probe baseline and progression/relapse tumor samples to identify mechanisms of resistance to PI3Kδ inhibition.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically confirmed follicular lymphoma grade 1-3A or marginal zone lymphoma by WHO criteria.

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter [LDi] to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥15 mm in LDi for nodal disease or ≥10 mm in LDi for extranodal lesions.[13]

3.1.3 Requires therapy based on: symptomatic disease, threatened end-organ dysfunction, compressive disease, cytopenias secondary to lymphoma, bulky disease (defined as any site ≥7 cm, or 3 or more sites ≥3cm), or steady progression.

3.1.4 For patients with follicular lymphoma: No prior systemic therapy for follicular lymphoma. Prior radiation to a single site of disease is allowed if completed at least 2 weeks prior to initiation of protocol therapy and there are additional sites of measurable disease outside of the radiation field.

3.1.5 For patients with marginal zone lymphoma: No prior systemic therapy for marginal zone lymphoma. Prior radiation or surgical resection is allowed if there are additional sites of measurable disease outside of the radiation field. Prior radiation must be completed at least 2 weeks prior to initiation of protocol therapy. Prior H. pylori eradication therapy is allowed.

3.1.6 Age ≥18 years.

3.1.7 ECOG performance status ≤2 (see Appendix A)

3.1.8 Participants must have adequate organ function as defined below:

– total bilirubin	<1.5 x institutional upper limit of normal (ULN) **or** <3 x ULN if considered due to Gilbert's syndrome
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits OR
– creatinine clearance	≥30 mL/min for participants with creatinine levels above institutional normal.

3.1.9 Participants must have adequate marrow function as defined below (unless abnormalities are considered related to marrow involvement by lymphoma):

- absolute neutrophil count ≥1,000/mcL (500/mcL is acceptable if due to marrow involvement by lymphoma)
- platelets ≥70,000/mcL(30,000/mcL is acceptable if due to marrow involvement by lymphoma)

3.1.10 Female participants who are not of child-bearing potential and female participants of child-bearing potential who have a negative serum pregnancy test. The serum pregnancy test must also be negative within 3 days prior to initial trial treatment, but this is not required for eligibility confirmation (i.e., the participant may be confirmed eligible and registered based on the negative serum pregnancy test obtained at screening). Female participants of child-bearing potential and all male partners, and male participants must consent to use a medically acceptable method of contraception throughout the study period and for a minimum of 1 year after the last dose of rituximab and for a minimum of 4 months after the last dose of umbralisib. See Appendix: CONTRACEPTION GUIDELINES AND PREGNANCY for additional information.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants who require immediate cytoreduction per the treating investigator.

3.2.2 For patients with H. pylori related gastric extranodal marginal zone lymphoma in the absence of t(11;18): Patient must have relapsed or refractory marginal zone lymphoma despite appropriate H. pylori eradication.

3.2.3 For patients with hepatitis C virus related marginal zone lymphoma: Patient must have relapsed or refractory marginal zone lymphoma despite appropriate treatment of hepatitis C virus infection.

3.2.4 Active systemic therapy for another malignancy within 2 years. Local/regional therapy with curative intent such as surgical resection or localized radiation is allowed if patient is deemed at low risk for recurrence by treating physician.

3.2.5 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 which in the opinion of the treating investigator has a low probability of requiring therapy within 5 years.

3.2.6 Corticosteroid therapy (prednisone >10 mg daily or equivalent) is not permitted within 7 days prior to study entry. Topical, or intra-articular or inhaled corticosteroids are permitted.

3.2.7 Prior allogeneic stem cell transplant.

3.2.8 Inflammatory bowel disease (such as Crohn's disease or ulcerative colitis)

3.2.9 Malabsorption syndromes

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

3.2.11 Known central nervous system involvement by lymphoma.

3.2.12 Evidence of histological transformation to large cell lymphoma.

3.2.13 History of allergic reactions attributed to compounds of similar chemical or biologic composition to umbralisib or rituximab.

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

3.2.15 Evidence of chronic active Hepatitis B (HBV, not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), active cytomegalovirus (CMV), or known history of HIV. If HBc antibody is positive, the patient must be evaluated for the presence of HBV DNA (by PCR). If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. If the patient is CMV IgG or CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. Patients with positive HBc antibody and negative HBV DNA via PCR are eligible, but prophylaxis with entecavir or lamivudine is recommended. Subjects who are CMV IgG or CMV IgM positive but who are CMV DNA negative by PCR are eligible, but antiviral prophylaxis should be considered per institutional protocol.

3.2.16 Any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:

3.2.16.1 Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV [see Appendix: NYHA Classifications])

3.2.16.2 Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, CHF, or myocardial infarction within 6 months of enrollment.

3.2.16.3 Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.

3.2.16.4 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.

3.2.16.5 Psychiatric illness/social situations that would limit compliance with study requirements

3.2.17 Known history of drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver.

3.2.18 Pregnant women are excluded from this study because rituximab is an agent with known potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with rituximab or umbralisib, breastfeeding should be discontinued if the mother is treated with rituximab or umbralisib. These potential risks may also apply to other agents used in this study.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

3.5 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

3.6 General Guidelines for Other Investigative Sites

N/A

3.7 Registration Process for Other Investigative Sites

N/A

4. TREATMENT PLAN

4.1 Treatment Regimen

A treatment cycle is defined as 28 consecutive days. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Umbralisib will be administered at 800 mg by mouth once daily on days 1-28 of cycles 1-24. Rituximab from a commercial supply will be administered at 375 mg/m2 by intravenous infusion on days 1, 8, 15, 22 of cycle 1, and may be administered at 375 mg/m2 by intravenous infusion or at 1400 mg by subcutaneous injection on day 1 of cycles 2 to 6, then every 8 weeks starting on day 1 of cycle 7 until completion of 24 cycles of umbralisib (i.e. every other cycle for 18 cycles or 9 doses, for a total of 15 doses of rituximab), or until progression or intolerance. There are no requirements regarding which study drug will be given first (i.e. umbralisib may be given either prior to or following rituximab administration).

4.2 Pre-Treatment Criteria

4.2.1 Cycle 1, Day 1

Cycle 1 Day 1 (C1D1) laboratories need to be reviewed before treatment if baseline/eligibility laboratories were drawn greater than 7 days prior to protocol treatment initiation. If laboratories are required on Cycle 1 Day 1, then:

Participants must have adequate organ function as defined in Section 3.1.8:

Participants must have adequate marrow function as defined in Section 3.1.9:

4.2.2 Subsequent Cycles

Patients should be assessed clinically for toxicity at each visit using the NCI CTCAE v5.0 (http://evs.nci.nih.gov/ftp1/CTCAE) grading scale. Dosing should occur only if a patient's clinical assessment and laboratory test values are acceptable (See **Section 5.1.1**). The CBC with differential and chemistries must be reviewed prior to treatment administration.

4.3 Agent Administration

4.3.1 Umbralisib administration

Umbralisib will be administered at 800 mg by mouth once daily on days 1-28 of cycles 1-24.

4.3.1.1 Supply:

TG Therapeutics. Immediately inform TG Therapeutics of any product quality concerns or questions via email to productquality@tgtxinc.com

4.3.1.2 Dispensing of umbralisib

Before dispensing, the site pharmacist or his/her representative must check that the umbralisib is in accordance with the product specifications and the validity is within the re-test date. Expiration memorandums will be provided by TG Therapeutics noting lot expiration dates. For questions about expiry, email productquality@tgtxinc.com. The pharmacist or his/her representative should record all umbralisib drug dispensations.

4.3.1.3 Method of administration:

Umbralisib will be administered orally once daily with food.

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. Patients must be provided drug in its original container.

Umbralisib should be taken at approximately the same time each day with food (within 30 minutes of a meal). Patients should be instructed to swallow the tablets as a whole and should not chew or crush them, and not to dissolve them in water or other liquid.

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

4.3.1.4 Potential drug interactions:

No drug interactions have been reported to date.

4.3.1.5 Prophylaxis:

Refer to Section 4.4.

4.3.1.6 Treatment compliance

Patients should be instructed to return all empty and partially filled bottles including any unused tablets when they return to the site.

The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at each protocol visit.

Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle and as needed.

4.3.2 Rituximab administration

Rituximab from a commercial supply will be administered per institutional guidelines at 375 mg/m2 by intravenous infusion on 1, 8, 15, 22 of Cycle 1 and may be administered at 375 mg/m2 by intravenous infusion or at 1400 mg by subcutaneous injection on day 1 of cycles 2 to 6, then every 8 weeks until completion of 24 cycles of umbralisib (i.e. every other cycle for 18 cycles starting on day 1 of cycle 7), or until progression or intolerance.

Rituximab will be administered at 375 mg/m2 by intravenous infusion on cycle 1 day 1. If the day 1 infusion cannot be completed within 1 day, the patient may receive the remainder of the infusion the following day on day 2. Actual body weight will be measured at each treatment day. Rituximab will be dosed per institutional standards for weight-based dosing, and acceptable options are as follows:

- Cycle 1 day 1 weight may be used for calculations of body surface area for subsequent treatment days unless it differs by 5% or more.
- Weight from each treatment day may be used to update calculations of body surface area to recalculate dose for each infusion.

Rituximab biosimilar may be substituted as per institutional guidelines.

4.3.2.1 Supply:

Commercial supply

4.3.2.2 Administration of Intravenous Rituximab and Pre-Medications:

Rituximab and associated pre-medications will be administered per institutional guidelines.

4.3.2.3 Administration Related Reactions:

Infusion/Administration Related Reactions (IRRs/ARRs) will be managed per institutional guidelines. Symptomatic infusion reactions, despite premedication, may be treated at the discretion of the treating physician, including but not limited to: temporary discontinuation of infusion, oral acetaminophen, corticosteroids, antihistamines, oxygen, and bronchodilators.

4.4 General Concomitant Medication and Supportive Care Guidelines

No drug interactions have been reported with Umbralisib. However, there is a potential to discover previously unidentified interactions between umbralisib with other concomitantly administered drugs. Therefore, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Infection prophylaxis: Choice of Pneumocystis and viral prophylaxis is per investigator discretion. If PCP or anti-viral therapy is not tolerated, alternate to a different PCP or anti-viral therapy, discontinue, or reduce dose/schedule as per investigator discretion.

- VSV/HSV Prophylaxis: Acyclovir 400 mg BID or equivalent.

- Hepatitis B Prophylaxis: For patients with positive HBc antibody and negative HBV DNA, prophylaxis with entecavir, lamivudine, or equivalent is required.

- Pneumocystis: Dapsone 100 mg daily, Bactrim DS 1 tablet 3x per week or SS 1 tablet daily, or an acceptable alternative according to institutional standards. Dapsone is preferred based on experience in TG therapeutics clinical trials, but choice of pneumocystis prophylaxis is at the discretion of the investigator.

- Prophylaxis against PJP and/or HSV/VZV may be started anytime during Cycle 1, up to and including Cycle 2 Day 1, at the discretion of the treating investigator.

4.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 24 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

4.6 Duration of Follow Up

Participants will be followed for 2 years after removal from protocol therapy or until death, whichever occurs first. Thereafter, patients may be followed for survival endpoints. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

5. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

5.1 Dose Delays and Modifications

5.1.1 Dose Delay/Modifications: Umbralisib

Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If the patient withdraws consent or has documented progression, an end of study visit should be completed. In cases of umbralisib dose delay, the

cycle day count will continue and subsequent assessments will remain on schedule.

TABLE 3: UMBRALISIB DOSE DELAY AND/OR MODIFICATIONS GUIDANCE

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 2 neutropenia	Maintain current dose.
Grade 3 neutropenia	Maintain current dose. If recurrent or persistent Grade 3, reduce to next lower dose level at discretion of the investigator.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay umbralisib until Grade ≤3 and neutropenic fever or infection is resolved; thereafter, resume at current dose. If recurrence after re-challenge, delay umbralisib until Grade ≤ 3 and/or neutropenic fever or infection is resolved; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose level
Grade 4 thrombocytopenia	Delay umbralisib until Grade ≤3; thereafter, resume at current dose. If recurrence after re-challenge, delay umbralisib until Grade ≤ 3; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator.
Pneumonitis	
Any grade	If pneumonitis is suspected, umbralisib treatment should be interrupted until the cause is determined. If pneumonitis is Grade 1 (asymptomatic), hold umbralisib treatment until complete resolution; thereafter, restart umbralisib at one lower dose level. If pneumonitis is symptomatic (any severity), umbralisib treatment should be permanently discontinued.
***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 level if tolerable and use anti-diarrheal medication. **NOTE**: If persistent grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ grade 1; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator. If recurrence after rechallenge, delay umbralisib until ≤ grade 1; thereafter, resume at current dose or next lower dose level at discretion of the investigator.
Diarrhea Grade ≥3	Withhold umbralisib until Grade ≤2. Resume at current dose or at next lower dose level at discretion of the investigator. If recurrence after rechallenge, delay umbralisib until ≤ grade 1; thereafter, resume at current dose or at next lower dose level at discretion of the investigator.
Colitis (all Grades)	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level.
Liver Toxicity (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Grade 1	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Monitor labs every 1-2 weeks.
Grade 2	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Begin supportive care: prednisone 0.5-1.0 mg/kg/day or equivalent per

	investigator discretion) **. Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off. If liver toxicity recurs to Grade 2: o Re-initiate steroids. o Monitor labs at least weekly until Grade 1. o Consider delaying umbralisib. o Once resolved to Grade ≤1 o If umbralisib was delayed, restart umbralisib at current dose. o Taper prednisone by 10 mg per week until off
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.
* Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc. **Supportive Care – Aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc. Important: Before initiating steroids, check for viral hepatitis or CMV infection.	
All Other Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level.
Grade ≥3	Withhold umbralisib until Grade ≤2. Thereafter, resume umbralisib at current dose. If recurrence after re-challenge, delay umbralisib until ≤ grade 2; thereafter, resume 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
Umbralisib	800 mg	600 mg	400 mg

A 3rd dose reduction to umbralisib 200 mg by mouth once daily is permitted with permission from the overall PI and TG Therapeutics.

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.

5.1.2 Dose Delay/Modification: Rituximab

No dose modifications for rituximab are permitted. Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If the patient withdraws consent or has documented progression, an end of study visit should be completed. In the event that umbralisib administration is delayed, rituximab may also be delayed at the discretion of the investigator.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

6.1.1 Expedited Reporting Guidelines

Use the protocol-specific participant ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor and the NCI **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

6.2 Expected Toxicities

6.2.1 Adverse Events Lists

6.2.1.1 Adverse Event List(s) for Umbralisib

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

6.2.1.2 Adverse Event List(s) for Rituximab and Rituximab Hyaluronidase

Severe infusion reactions/hypersensitivity reactions: hypotension, angioedema, hypoxia or bronchospasm. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Additional AEs include fevers, renal toxicity, rash, neutropenia, infection including progressive multifocal leukoencephalopathy, hepatitis B reactivation, and tumor lysis syndrome. Those patients receiving Rituximab Hyaluronidase may also experience injection site erythema and/or pain.

6.3 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **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.

6.4 Adverse Event Reporting

6.4.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

6.4.2 Investigators **must** report to the Overall PI any severe adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

6.4.3 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

6.4.4 Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE	Adverse	Grade	Hospitalization/	Attribution	Comments

SOC	Event		Prolongation of Hospitalization		
N/A	N/A	N/A	N/A	N/A	N/A

6.5 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

6.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

6.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

6.8 Serious Adverse Event Reporting to TG Therapeutics, Inc.

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 (copy gabriel.green-lemons@tgtxinc.com and donna.gesumaria@tgtxinc.com) within 24 hours of the first knowledge of the event by the treating physician or research personnel on an SAE Form (MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable). Include the TG Therapeutics tracking number, TGR-NTG-005, on the SAE report to TG Therapeutics and indicate whether or not the SAE was designated a SUSAR.

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

Pregnancy

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).

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

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must 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 following the same process described for reporting SAEs to TG Therapeutics, Inc. Include the TG Therapeutics, Inc. tracking number, TGR-NTG-005, on the Pregnancy Report Form and include an assessment of the causal relationship to the study drug. Male subjects must contact the investigator immediately if their female partner becomes pregnant, and the investigator must submit a Pregnancy Report Form to TG Therapeutics, Inc. within 24 hours as described above.

Consent will be obtained from the pregnant female subject/male subject's partner to allow the pregnancy to be followed up for the full duration of the pregnancy (or until spontaneous abortion or voluntary termination), to collect the outcome with details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, as applicable. Additionally, medical information must be collected on the newborn for 6 months after birth, as permitted by local regulations.

Any SAE experienced during pregnancy must be reported to TG Therapeutics, Inc. Congenital anomalies/birth defects **always** meet SAE criteria, and must therefore be expeditiously reported as an SAE to TG Therapeutics, Inc. SAEs experienced during pregnancy and congenital anomalies/birth defects must be reported to TG Therapeutics, Inc. on the SAE Report Form within 24 hours of the first knowledge of the event by the investigator or research personnel following the same process as described above for SAEs.

Abortions (spontaneous, accidental, or therapeutic) must also be reported to TG Therapeutics at safety@tgtxinc.com within 24 hours of awareness on a Pregnancy Report Form as described above. Please see APPENDIX: 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 umbralisib 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 an umbralisib overdose occurs, patients should stop umbralisib dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

7. PHARMACEUTICAL INFORMATION

7.1 Umbralisib

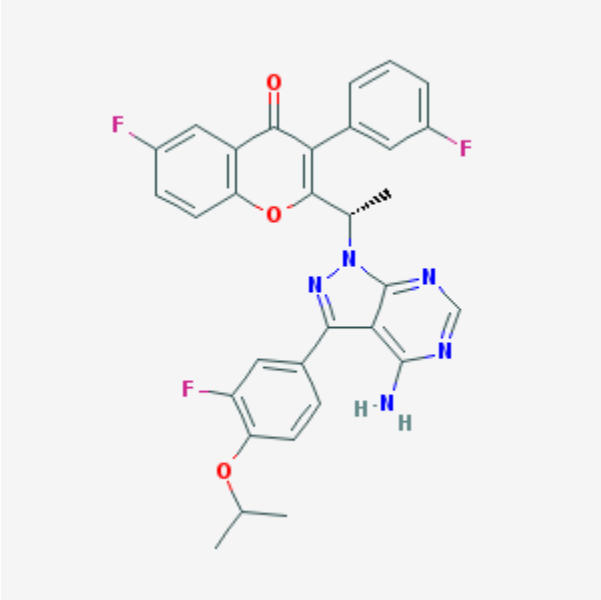
7.1.1 Description

Umbralisib (TGR-1202) is a highly-specific and orally available inhibitor of phosphoinositide-3-kinase (PI3K) delta (δ) and casein kinase-1 epsilon (CK1ε) with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K.

PubChem CID: 72950888

Molecular Formula: $C_{31}H_{24}F_3N_5O_3$

Molecular Weight: 571.56 g/mol



Provide basic pharmacokinetic information including mechanism of clearance, plasma t ½ and relevant drug interactions.

7.1.2 Form

Umbralisib is provided in 200 mg tablets.

Umbralisib is provided in HDPE bottles each containing 30 tablets and a silica gel canister as a desiccant.

7.1.3 Storage and Stability

Store between 20°C and 25°C. Excursions permitted 15°C to 30°C. Do not freeze.

7.1.4 Compatibility

N/A

7.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.1.6 Availability

Umbralisib is available from TG Therapeutics.

7.1.7 Preparation

Umbralisib is provided in HDPE bottles each containing 30 tablets and a silica gel canister as a desiccant.

7.1.8 Administration

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

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

7.1.9 Ordering

Umbralisib (TGR-1202) is available from TG Therapeutics. Please allow 5 to 7 business days between drug ordering and drug arrival. Please direct drug orders to ISTdrugorder@tgtxinc.com. The email should include the following:

- Requested quantity of TG Therapeutics study drug(s)
- Date needed
- Principal Investigator name
- Study title
- Investigational drug pharmacy shipping address
- TG Therapeutics tracking number, TGR-NTG-005

Upon receipt of this shipment, the Pharmacist or the appropriate person at the site should update the accountability forms for umbralisib. If there is any abnormality in the supplied bottles, the Pharmacist or the appropriate person must document it during the acknowledgement of receipt and contact TG Therapeutics at

productquality@tgtxinc.com.

7.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

7.1.11 Destruction and Return

Unused supplies of umbralisib will be destroyed or returned to TG therapeutics. Any expired supplies of umbralisib will also be destroyed or returned to TG therapeutics.

7.1.12 Pharmacokinetic Studies

7.1.12.1 Healthy Subject Pharmacokinetic Studies

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

7.1.13 TGR-1202-PK101: Food Effect

Study TGR-1202-PK 101 was two-period, randomized, two-way crossover, drug-food, drug-gender interaction study in 24 healthy subjects (12 males and 12 females) to assess the mean plasma umbralisib concentration over time following a single oral dose of 200 mg of umbralisib under fasting and fed condition using the original formulation. In general, administration of umbralisib under fed conditions results in a higher rate of exposure relative to when the product was given under fasting conditions.

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

Parameters	Geometric LS Means		% Geometric	Confidence Interval
	Fasting	Fed		
AUC0-t (ng·hr/mL)	6029.87	9692.02	160.73	140.25 – 184.21

AUC0-inf	8391.35	14047.17	167.40	141.59 – 197.92
Cmax (ng/mL)	176.78	483.15	273.31	234.04 – 319.17

Food increased both the extent and rate of exposure of umbralisib. The extent (AUC0-t) and total extent (AUC0-inf) of exposure increased by 61% and 67%, respectively, when umbralisib was administered under fed conditions compared to fasting conditions. The peak plasma levels of umbralisib increased by over 173% when umbralisib was administered with food.

Using these mean values, a 334 mg oral dose of umbralisib under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of umbralisib under fed conditions in terms of exposure based on AUC0-inf.

7.1.14 TGR-1202-PK102: Formulation Effect

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

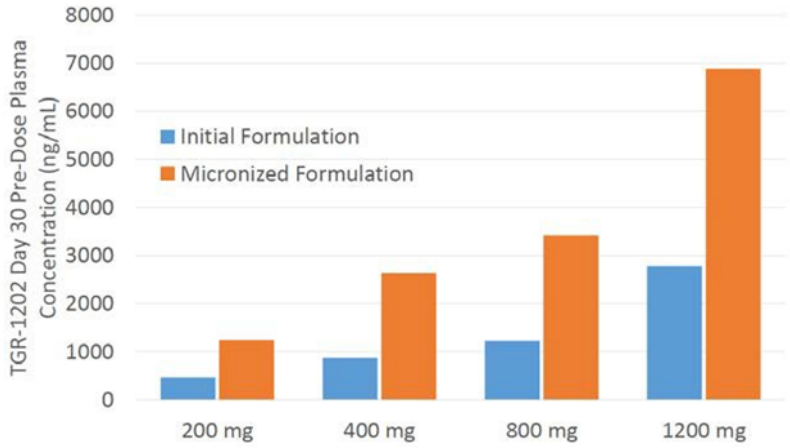
Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Original Formulation	Micronized Formulation		
AUC0-t (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95
AUC0-inf (ng·hr/mL)	7715.67	12378.19	160.43	146.49 – 175.70
Cmax (ng/mL)	166.20	371.70	223.65	202.33 – 247.20

The micronized drug product formulation increased both the extent and rate of exposure of umbralisib under fasted conditions. The extent (AUC0-t) and total extent (AUC0-inf) of exposure both increased by 60%, respectively, following administration of the modified drug product formulation relative to original drug product formulation. The Peak plasma (Cmax) levels of umbralisib increased by over 124% following administration of the micronized drug product formulation relative to original drug product formulation under fasted conditions.

Using these mean values, a 320 mg oral dose of umbralisib in the original formulation under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of the original formulation umbralisib under fasted conditions in term of exposure based on AUC0-inf.

The improved exposure seen with the micronized formulation of umbralisib was confirmed in

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



7.2 Rituximab (Intravenous)

7.2.1 Description

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG1 κ immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analaysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM.

7.2.2 Form

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

7.2.3 Storage and Stability

Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from

direct sunlight.

7.2.4 Compatibility

No incompatibilities between Rituximab and polyvinylchloride or polyethylene bags have been observed.

7.2.5 Handling and Preparation

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Use appropriate aseptic technique. Withdraw the necessary amount of Rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 12 hours.

7.2.6 Availability

Rituximab is approved by the FDA for treatment of low-grade B cell lymphomas and is widely used for the treatment of chronic lymphocytic leukemia. Rituximab for this study will be from commercial supply.

7.2.7 Administration

Rituximab will be administered per institutional guidelines.

Infusion and hypersensitivity reactions may occur. Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion. No specific pre-hydration is required.

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments approximately every 30 minutes, to a maximum of 400 mg/hr.

Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of

rituximab therapy

Patients without significant hypersensitivity reactions to the induction rituximab treatments may receive the standard dose (375mg/m2) maintenance treatments per the DFHCC accelerated infusion protocol for rituximab. Under the standard accelerated infusion protocol, Rituximab is administered at an initial rate of 20 percent of the total dose over 30 minute, followed by the remaining 80 percent of the total dose over 60 minutes. For patients who experienced a significant hypersensitivity reaction with the first or previous cycle, initiate rate at 50 mg/hr and follow instructions for the first infusion.

7.2.8 **Ordering**

Rituximab is approved by the FDA for treatment of low-grade B cell lymphomas including follicular lymphoma. Rituximab for this study will be from commercial supply.

7.2.9 **Pharmacokinetics**

The mean serum half-life of rituximab, as shown below, has been reported for rituximab given at a dose of 375 mg/m2.[2] Wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20 positive (normal and malignant) B-cell populations upon repeated administrations.

Infusion #	Mean serum half-life (range)
After the 1st infusion	33.2 hours (11.1 – 53.1)
After the 4th infusion	76.6 hours (26.4 – 106.0)

Peak and trough levels were reported for 166 patients given rituximab as an IV infusion at weekly intervals for four doses at a dose of 375 mg/m2.[3] The levels were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden.

7.3 **Rituximab hyaluronidase human (Subcutaneous)**

7.3.1 **Description**

RITUXIMAB HYALURONIDASE is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is

produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

7.3.2 **Form**

RITUXIMAB HYALURONIDASE (rituximab and hyaluronidase human) Injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous administration.

RITUXIMAB HYALURONIDASE is supplied as 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL in single-dose vials or 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL in single-dose vials. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

7.3.3 **Storage and Stability**

RITUXIMAB HYALURONIDASE (rituximab and hyaluronidase human) Injection formulated for subcutaneous injection is supplied as a sterile preservative-free liquid solution in a single-dose vial. The following configurations are available:

Individually packaged single-dose vials:

- RITUXIMAB HYALURONIDASE 1,400 mg/23,400 Units (NDC 50242-108-01) providing 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL
- RITUXIMAB HYALURONIDASE 1,600 mg/26,800 Units (NDC 50242-109-01) providing 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL

Storage and Stability Store RITUXIMAB HYALURONIDASE vials in the refrigerator at 2ºC–8ºC (36ºF–46ºF) in the original carton to protect from light. Do not freeze.

7.3.4 **Compatibility**

N/A

7.3.5 **Handling and Preparation**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

RITUXIMAB HYALURONIDASE is ready to use. To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration.

RITUXIMAB HYALURONIDASE is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles. Use the product immediately.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. RITUXIMAB HYALURONIDASE should be a clear to opalescent and colorless to yellowish liquid. Do not use vial if particulates or discoloration is present.

7.3.6 **Availability**

RITUXIMAB HYALURONIDASE is approved by the FDA for treatment of low-grade B cell lymphomas including follicular lymphoma. Rituximab for this study will be from commercial supply.

7.3.7 **Administration**

All patients must receive at least one full dose of a rituximab product by intravenous infusion before starting treatment with RITUXAN HYCELA.

RITUXIMAB HYALURONIDASE will be administered per institutional guidelines.

Infusion and hypersensitivity reactions may occur. Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab. Premedication may attenuate administration-related events. Since transient hypotension may occur during administration, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion. No specific pre-hydration is required.

Administration

- Inject RITUXIMAB HYALURONIDASE into the subcutaneous tissue of the abdomen over approximately 5–7 minutes and never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.
- Inject 11.7 mL of RITUXIMAB HYALURONIDASE 1,400 mg/23,400 Units vial (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously into the abdomen over approximately 5 minutes.
- Inject 13.4 mL of RITUXIMAB HYALURONIDASE 1,600 mg/26,800 Units vial (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously into the abdomen over approximately 7 minutes.

If administration of RITUXIMAB HYALURONIDASE is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen.

Observe patients for at least 15 minutes following RITUXIMAB HYALURONIDASE administration.

During treatment with RITUXAN HYCELA, do not administer other medications for subcutaneous use at the same sites as RITUXAN HYCELA.

After the solution of RITUXIMAB HYALURONIDASE is withdrawn from the vial, it should be labeled with the peel-off sticker and used immediately. If not used immediately, prepare in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store the solution of RITUXIMAB HYALURONIDASE in the refrigerator at 2°C–8°C (36°F–46°F) up to 48 hours and subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.

7.3.8 **Ordering**

7.3.9 RITUXIMAB HYALURONIDASE is approved by the FDA for treatment of low-grade B cell lymphomas including follicular lymphoma. Rituximab for this study will be from commercial supply.

8. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

8.1 Laboratory Correlative Studies

PI3Kδ inhibitors are highly active in patients with FL, but most patients will ultimately progress despite ongoing PI3Kδ inhibition. While several mechanisms of resistance to PI3K inhibitors have been described, including feedback activation of AKT or cross-talk pathways, the mechanisms of resistance to PI3Kδ inhibition in patients with FL is poorly understood. We will therefore probe baseline and progression/relapse tumor samples among patients with FL to identify mechanisms of resistance to PI3Kδ inhibition.

8.1.1 Identifying mechanisms of resistance to PI3Kδ inhibition in follicular lymphoma

8.1.1.1 Collection of baseline tumor specimen: If a fresh tumor biopsy is planned during screening and sufficient tissue is procured, the fresh tumor biopsy specimen will be allocated for correlatives. If a fresh tumor biopsy specimen is unavailable, then previous diagnostic formalin-fixed, paraffin-embedded (FFPE) tumor specimens will be requested. If multiple previous FFPE tumor specimens are available, then multiple baseline tumor specimens may be subjected to testing. A buccal swab will also be collected for correlatives.

8.1.1.2 Collection of relapse/progression specimen: If a fresh tumor biopsy is planned at relapse/progression, tumor biopsy specimen (either banked FFPE tumor specimen or fresh tumor specimen) will be allocated for correlatives.

8.1.1.3 Planned correlative analyses: Baseline and relapse/progression specimens as well as paired normal specimens (buccal swab) will be subjected to whole exome sequencing (WES). Any fresh tumor specimens may also be subjected to RNAseq.

8.1.1.4 Samples (blood, bone marrow, tissue, etc.) may not be taken from subjects and stored for future research that is not defined within this protocol without a contractual agreement between the institution and TG Therapeutics, Inc. to govern the ensuing research prior to its conduct. Investigators and institution may also not provide samples taken from subjects to anyone outside of their institution for any purpose without prior written approval by TG Therapeutics, Inc.

8.1.1.5 Additional details regarding collection, processing, and delivery of specimens for correlative analyses are included in the Lab Manual.

9. STUDY CALENDAR

Assessments must be performed prior to administration of any study agent. In the event that the participant's condition is deteriorating in the opinion of the investigator, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

9.1 Study Calendar

Procedures	Screening	Cycle 1				Cycle 2-6	Cycles 7, 9, 11, 13, 15, 17, 19, 21, 23	EOT 28d +/- 14d after last treatment	Follow Up Every 12 weeks +/- 14 days	Off Study +/- 14 days
Window		+/- 3 Days				+/- 7 days	+/- 7 days			
Study Day(s)	**-45 to 0[1]**	**1***	**8**	**15**	**22**	**1**	**1**			
Umbralisib[9]		**Umbralisib Administration through Cycle 24**								
Rituximab		**X**	**X**	**X**	**X**	**X**	**X**			
Informed consent	X									
Medical history	X									
Concurrent medications	X	X	X	X	X	X	X	X		
Adverse Event Evaluation	X	X	X	X	X	X	X	X[6]		
Vital signs	X	X	X	X	X	X	X	X		
Physical exam	X		X			X	X	X		
Height	X									
Weight	X	X[2]	X	X	X	X	X			
ECOG performance status	X	X[2]				X	X	X	X	X
CBC with differential	X[1]	X[2]	X	X	X	X	X	X	X	X
Comprehensive metabolic panel (sodium, potassium, chloride, CO2, BUN, creatinine, glucose, calcium, total bilirubin, alkaline phosphatase, AST, ALT)	X[1]	X[2]	X	X	X	X	X	X	X	X
LDH	X									
B2-microglobulin	X									
Serum protein electrophoresis and immunofixation	X									
IgG, IgA, IgM	X							X	X	X
EKG	X									
Serum pregnancy test (B-HCG)	X[3]	X[3]								
HIV, Hepatitis B and C, and CMV testing	X[4]									
CMV +/- HBV/HCV surveillance[8]	X[4]					X[8]	X[8]	X[8]		
PET-CT imaging	X					X[5]	X[5]	X[5]	X[5]	
Tumor specimen for correlative studies[7]	X[7]					X[7]	X[7]	X[7]	X[7]	X[7]
Buccal swab for correlative studies	X[7]									

* - TLS laboratories (BUN/Creatinine, Phosphorus, Calcium, Uric Acid, LDH) will be obtained between at 24-72 hours in patients considered at high risk for TLS (e.g. high disease burden, renal dysfunction, elevated uric acid pretreatment) per the treating investigator.

1- CBC with differential and comprehensive metabolic panel are required for eligibility. If done for eligibility/screening but not within 7 days of initiation of therapy, then must be repeated within 7 days prior to date of protocol therapy start.

2- Not necessary if screening assessments performed within 7 days of treatment initiation

3- Not necessary if male or woman who is not of childbearing potential. The Cycle 1 Day 1 serum pregnancy test for females of childbearing potential must be performed within 3 days of Cycle 1 Day 1.

4- HIV, CMV, Hepatitis B and C testing may be performed within 30 days prior to date of protocol therapy start. See Exclusion Criteria for additional information.

5- CT chest/abdomen/pelvis (and neck if warranted) and FDG-PET scan are required during Screening; after 2 months (C3D1); after 6 months (C7D1); then every 6 months during umbralisib maintenance therapy (C13D1, C19D1, EOT); then every 12 months during post-treatment surveillance. If patient achieves PET negative CR at any time on study, FDG-PET scan is not required for subsequent response evaluation.

6- If clinically significant adverse event or abnormal result is observed that is not resolved by the end-of study visit, continue to monitor and record through 30 days after umbralisib discontinuation.

7- Tumor specimens for correlative studies will include either banked formalin-fixed, paraffin-embedded (FFPE) specimens or fresh tumor biopsy specimen (if obtained for a standard clinical indication per the discretion of the investigator). In patients who do not have adequate available tumor specimen for correlative studies, a biopsy is NOT required.

8- CMV surveillance by PCR on Day 1 of Cycles 1-6, then on C7D1, C11D1, C15D1, C19D1, and C23D1. For subjects with positive HCV antibody and negative/undetectable HCV RNA, HCV RNA (PCR) will be obtained on Day 1 of Cycles 1-6, then on C7D1, C11D1, C15D1, C19D1, and C23D1. For subjects with positive HBc antibody and negative HBV DNA via PCR who are on prophylaxis with entecavir or lamivudine as recommended, HBV DNA (PCR) will be obtained on Day 1 of Cycles 1-6, then on C7D1, C11D1, C15D1, C19D1, C23D1, and at each follow up visit.

9- Subjects will be dispensed a 1 month supply of study drug for Cycles 1-6 and a 2 month supply of study drug for subsequent cycles.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect: 2014 Lugano Criteria

10.1.1 Selection of Target Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

1. Clearly measurable in two diameters (longest diameter [LDi] and shortest diameter) at baseline
    a. All nodal lesions must measure > 1.5 cm in longest diameter regardless of short axis measurement
    b. All measurable extranodal lesions should have a longest tumor diameter ≥ 1.0 cm
2. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target lesions
3. If possible, the lesions should be from disparate regions of the body
4. Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

10.1.2 Selection of Non-Target Lesions

Non-target lesions will be qualitatively assessed at each subsequent time point. All sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions.

Examples of non-target lesions include:

1. All bone lesions, irrespective of the modality used to assess them
2. Lymphangitis of the skin or lung
3. Cystic lesions
4. Splenomegaly and hepatomegaly (all lymphomas)
    a. Cutoff for splenomegaly of more than 13 cm
    b. Diffusely increased or focal uptake, with or without focal or disseminated nodules, supports spleen or liver involvement
5. Irradiated lesions
6. Measurable lesions beyond the maximum number of six
7. Groups of lesions that are small and numerous
8. Pleural/pericardial effusions and/or ascites

a. Effusions, ascites, or other fluid collections will be followed as non-target lesions

b. At each assessment point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.

c. Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions and should be assessed

Response should be determined on the basis of radiographic and clinical evidence of disease. Assessment by PET should follow the criteria described by Cheson et al[13] which is summarized in the table below.

10.1.2.1 Revised Criteria for Response Assessment from Cheson et al 2014

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

Response and Site	PET-CT–Based Response	CT-Based Response
No Response or Stable Disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive Disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New Lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

[a] *Measured dominant lesions: up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).*

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

10.1.2.2 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.2.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

10.1.3 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.1.4 Progression-Free and Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last evaluation.

10.1.5 Response Review

All responses be reviewed by the Tumor Imaging Metrics Core.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.2.1 Safety Rules: Triggers for enrollment pause and DSMC review

If an SAE occurs in 5 or more of the first 15 patients enrolled in Stage I of this protocol, we will pause enrollment and the DSMC will review and monitor toxicity from this study to provide guidance regarding whether to continue enrollment or terminate the study.

If an SAE occurs one-third or more of the number patients enrolled in the study at any timepoint during Stage II, then we will pause enrollment and the DSMC will review and monitor toxicity from this study to provide guidance regarding whether to continue enrollment or terminate the study.

If any death occurs on study, we will pause enrollment and the DSMC will review and monitor toxicity from this study to provide guidance regarding whether to continue enrollment or terminate the study.

11.3 Collaborative Agreements Language

N/A

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

12.1.1 Primary efficacy endpoints:

1. To describe the complete response rate

12.1.2 Secondary efficacy endpoints:

1. To describe the overall response rate
2. To estimate the progression-free survival and overall survival

12.1.3 Safety endpoints:

1. To describe the nature, frequency, severity, and timing of adverse events

12.2 Sample Size, Accrual Rate and Study Duration

The study will use a Simon two-stage design to allow for early termination for lack of efficacy. A complete response rate (CRR) of at least 50% will be considered promising whereas a CRR of 30% or less will be considered non-promising.

Initially, an accrual goal of fifteen eligible patients would be enrolled to stage one. If four or fewer complete responses are observed, the regimen would be considered non-promising, and the study will stop early for lack of efficacy. If five or more complete responses are observed within the first fifteen patients, an additional 26 patients would be entered to stage two for a total sample size of 41. If at least sixteen complete responses are observed in 41 patients, the study would be considered successful and the regimen worthy of further study. If the total number of complete responses observed is fifteen or fewer, the regimen would be considered non-promising.

Though it was initially expected that about 41 people would take part in this research study, the current study has stopped enrolling patients earlier than planned. No new patients will be enrolled in the future.

The study has an overall power and type-I error of 0.902 and 0.120, respectively. With a total size of 41 patients, the two-stage exact 95% confidence interval for CRR will be no wider than +/- 20%. If the true CRR is 30%, the regimen will be considered non-promising with probability 0.880; furthermore, the study will stop early with a probability of 0.515 if the true CRR is 30%. With the stage-one sample size of fifteen patients, the exact 95% confidence interval for CRR will be no wider than +/- 26%. If the true CRR is 50%, the regimen will be considered non-promising with probability 0.098 (type-II error); the study will stop early with a probability of 0.059 if the true CRR is 50%.

The study duration will be 4 years; 2 years of accrual and 2 years of follow-up on the last participant enrolled.

UPDATE:
A recent analysis of a Phase 3, randomized, 4-arm study for patients with CLL (Study UTX-TGR-304 – EudraCT: 2015-005758-36; NCT02612311) compared overall survival (how long patients live following treatment on the study) and the results indicated inferior overall survival among patients treated with ublituximab + umbralisib, ublituximab, or umbralisib compared to those treated with obinutuzumab + chlorambucil. The overall survival analysis is based on the time to death from any cause, including the disease, the treatment, or any other reason such as COVID-19 or other medical conditions. At the time of the analysis 57 patients (27%) treated with ublituximab + umbralisib (Arm A) have died, 53 patients (25%) treated with obinutuzumab + chlorambucil (Arm B) have died, 29 patients (32%) treated with ublituximab alone (Arm C) have died, and 33 patients (36%) treated with umbralisib alone (Arm D) have died. Given these data, TG Therapeutics is no longer supporting investigator-initiated trials of umbralisib in oncology, and this study we have permanently stopped accrual to this study. However, patients who remain on therapy and demonstrate ongoing clinical benefit and tolerability may remain on protocol therapy. We felt this was an appropriate option for patients for several reasons. First, stopping umbralisib may result in loss of disease control for some patients, so there is risk to treatment discontinuation in a patient in ongoing response. Second, there were important differences between the UTX-TGR-304 study and our study: (1) UTX-TGR-304 patients received treatment until progression or intolerance, while patients in this study stop therapy after two years; (2) UTX-TGR-304 patients had CLL which itself is associated with immune dysregulation and increased infection risk; and (3) In the UTX-TGR-304 trial, the control arm was obinutuzumab-chlorambucil without maintenance therapy, whereas in our study the alternative standard therapy would be a different chemoimmunotherapy regimen with or without maintenance CD20 antibody therapy. Therefore, while we have decided to permanently close this study to enrollment. We will not have sufficient accrual to evaluate the primary endpoint as detailed above. Therefore, we plan to report clinical efficacy and safety data after the last enrolled patient is on therapy for at least 6 months, along with the correlative data. These data will be hypothesis generating only.

12.3 Accrual targets by Gender, Racial, and Ethnic Category

The accrual targets by ethnic and racial category reflect the expected accrual over the life of the study and resemble the gender, ethnic, and racial composition of follicular lymphoma patients in the US population.

Accrual Targets							
Ethnic Category	**Sex/Gender**						
	Females		**Males**			**Total**	
Hispanic or Latino	5	+	4		=	9	
Not Hispanic or Latino	16	+	16		=	32	
Ethnic Category: Total of all subjects	21	+	20	(B1)	=	41	(C1)
Racial Category							
American Indian or Alaskan Native	0	+	0		=	0	
Asian	1	+	1		=	2	
Black or African American	1	+	1		=	2	
Native Hawaiian or other Pacific Islander	0	+	0		=	0	
White	19	+	18		=	37	
Racial Category: Total of all subjects	21	+	20		=	41	
	(A1 = A2)		(B1 = B2)			(C1 = C2)	

12.4 Stratification Factors

N/A

12.5 Interim Monitoring Plan

We will use a Simon two-stage design to allow for early termination for lack of efficacy (See Section 12.2).

12.6 Analysis of Primary Endpoints

See Section 12.2 for description of the statistical methodology used to address the study's primary aim.

12.7 Analysis of Secondary Endpoints

12.7.1 Complete response rate

Patients will have their response classified per the 2014 Lugano criteria (see Section 10). The frequency of complete response will be tabulated and summarized descriptively.

12.7.2 Progression-free and overall survival

Median progression-free survival and overall survival will be summarized using Kaplan-Meier method with time of registration as time origin. Participants will be followed for 2 years after removal from protocol therapy or until death, whichever occurs first. Participants will be censored at the date of their last evaluation.

12.7.3 Nature, frequency, severity, and timing of adverse events

Patients will have their toxicities graded and reported at every visit according to criteria listed in CTAE ver. 5.0. The nature, frequency, severity, and timing of adverse events will be tabulated and summarized descriptively.

12.8 Reporting and Exclusions

12.8.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

12.8.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study must be assessed for response/outcome to therapy, unless they withdraw consent prior to first response evaluation. Participants who withdraw consent prior to first response evaluation will be replaced.

13. PUBLICATION PLAN

13.1 Final report

The final study results should be made public within 24 months of reaching the end of the study. TG Therapeutics is no longer supporting investigator-initiated trials of umbralisib in oncology, due to results of a recent analysis of a phase 3, randomized, 3-arm study for patients with CLL (UTX-TGR-304; NCT02612311) in which patients who received ublituximab + umbralisib, umbralisib, or ublituximab, had inferior all-cause overall survival compared to obinutuzumab + chlorambucil. We will not meet accrual goals to evaluate the primary endpoint with adequate power. Therefore, we plan to complete correlative analyses and publish the final report in a peer-reviewed journal once the last enrolled patient is at least 6 months on treatment. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study. All manuscripts, abstracts, or other presentation materials generated must be reviewed by TG Therapeutics prior to submission.

14. PROTOCOL AMENDMENTS

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

REFERENCES

1. Burris HA, Flinn IW, Patel MR, Fenske TS, Deng C, Brander DM, et al. Umbralisib, a novel PI3Kδ and casein kinase-1ε inhibitor, in relapsed or refractory chronic lymphocytic leukaemia and lymphoma: an open-label, phase 1, dose-escalation, first-in-human study. *Lancet Oncol*. 2018;19(4):486-496.
2. Maloney DG, Grillo-López AJ, Bodkin DJ, White CA, Liles TM, Royston I, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *J Clin Oncol*. 1997;15(10):3266-3274.
3. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16(8):2825-2833.
4. Colombat P, Salles G, Brousse N, Eftekhari P, Soubeyran P, Delwail V, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. *Blood*. 2001;97(1):101-106.
5. Witzig TE, Vukov AM, Habermann TM, Geyer S, Kurtin PJ, Friedenberg WR, et al. Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group. *J Clin Oncol*. 2005;23(6):1103-1108.
6. Hainsworth JD, Litchy S, Burris HA, Scullin DC, Corso SW, Yardley DA, et al. Rituximab as First-Line and Maintenance Therapy for Patients With Indolent Non-Hodgkin's Lymphoma. *J Clin Oncol*. 2002;20(20):4261-4267.
7. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105(4):1417-1423.
8. Coiffier B, Lepage E, Brière J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma. *N Engl J Med*. 2002;346(4):235-242.
9. Davis TA, Grillo-López AJ, White CA, McLaughlin P, Czuczman MS, Link BK, et al. Rituximab Anti-CD20 Monoclonal Antibody Therapy in Non-Hodgkin's Lymphoma: Safety and Efficacy of Re-Treatment. *J Clin Oncol*. 2000;18(17):3135-3143.
10. Davies A, Merli F, Mihaljević B, Mercadal S, Siritanaratkul N, Solal-Céligny P, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2017;4(6):e272-e282.
11. Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*.

2014;370(11):1008-1018.
12. Dreyling M, Morschhauser F, Bouabdallah K, Bron D, Cunningham D, Assouline SE, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol*. 2017;28(9):2169-2178.
13. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol*. 2014;32(27):3059-3067.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B 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 a minimum of 1 year after the last dose of rituximab and for a minimum of 4 months after the last dose of umbralisib. Effective contraception is defined as either:

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

The following are **unacceptable** forms of contraception for 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, but this is not required for eligibility confirmation.

Fertile Males

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment and for a minimum of 1 year after the last dose of rituximab and for a minimum of 4 months after the last dose of umbralisib. 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 6 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

APPENDIX C 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.