Protocol Title

Phase Ib/II trial of Ublituximab with CHOP (U2-CHOP) followed by U2 maintenance (U2-CHOP-U2) in previously untreated Mantle Cell Lymphoma (MCL)

Study Protocol & Statistical Analysis Plan

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Table of Contents

PROTOCOL SYNOPSIS

PROTOCOL INFORMATION	
Title: U2-CHOP-U2 in MCL: Phase Ib/II trial of Ublituximab with CHOP (U2-CHOP) followed by U2 maintenance (U2-CHOP-U2) in previously untreated Mantle Cell Lymphoma (MCL)	
Objectives	**Primary Objective:** **Phase Ib:** To determine the safety of Umbralisib and Ublituximab in combination with CHOP chemotherapy for newly diagnosed MCL **Phase II:** CRR: To determine the efficacy of U2-CHOP in terms of Complete Response rates (CRR) in patients with untreated MCL after induction phase (6 cycles of U2-CHOP) by PET/CT response assessment criteria by Cheson 2014 (appendix) **Secondary Objectives:** **Phase II:** To determine Overall response rate (ORR=CR+PR) of the induction treatment with U2-CHOP in untreated MCL To determine Overall Survival (OS) at 3 years To determine Progression Free Survival (PFS) at 3 years To determine the rate of disease control (CR+PR+SD) at 3 years **Exploratory:** To determine the frequency of MRD negative (MRD-) disease at the end of induction treatment with U2-CHOP.
Study Design	Single arm, multi-center, open label Phase II trial with safety lead in Phase Ib.
Study Population	Adult patients with newly diagnosed MCL (Stage II-IV).
Inclusion Criteria	• Males or female patients ≥18 years of age

	• Diagnosis if MCL (Stage II, III, IV) as supported by histology and over expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) by FISH (fluorescent in situ hybridization) with indication of initiation of therapy. • At least one LN of >1.5 cm size as index/measurable site of disease • No prior therapy for MCL • Not eligible for bone marrow transplantation (assessed by treating physician due to comorbidities) or not interested in bone marrow transplant (clear documentation of patient's unwillingness to pursue transplant) • Eastern cooperative Oncology Group (ECOG): 0,1 or 2 (Appendix) • Absolute neutrophil count (ANC) ≥1500 (≥1000 if bone marrow involvement with MCL) within 28 days prior to initiation of therapy • Platelets ≥100000 cells/μL (≥75000 cells/μL if bone marrow involvement with MCL) within 28 days prior to initiation of therapy • Hemoglobin ≥9.0 gm/dL (≥8.0 gm/dL if bone marrow involvement with MCL) within 28 days prior to initiation of therapy • Alanine transaminase (ALT)/Aspartate Transaminase (AST) <3.0 X Upper limit of Normal (ULN) within 28 days prior to initiation of therapy • Total Bilirubin <2 X ULN within 28 days prior to initiation of therapy • Calculated Creatinine Clearance ≥35 mL/min by Cockcroft-Gault Equation • Male patients must agree to use an acceptable method of contraception for the entire duration of study. • All patients (or their legal representative) must have signed an informed consent indicating that they are willing to participate in the study and are willing to follow the procedure required by the study in accordance with federal, local and institutional guidelines. • Female patients who are not of child-bearing potential (see Appendix: CONTRACEPTION GUIDELINES AND PREGNANCY), and female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of either study drug.

Exclusion Criteria	• Any prior anti-neoplastic therapy for MCL • CNS involvement by MCL • Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or localized thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas. • If patient has received prior anthracycline therapy, the cumulative anthracycline dose should be <150mg/m2 of doxorubicin equivalent • H/O prior Allogeneic transplantation or autologous stem cell transplantation for any other reason. • Use of immunosuppressive therapy (e.g. cyclosporine A, tacrolimus or high dose steroids). Patients receiving steroids must be at a dose of <10mg/day prednisone (or equivalent) within 7 days of the first day of the study treatment administration. Patients are allowed to use topical or inhaled corticosteroids. • Concurrent any anticancer therapy for any other cancer (chemotherapy, radiation, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy or tumor embolization). • Use or expected use during the study of any prohibited medications including potent CYP3A4 inhibitors, inducers, substrates (appendix) within 14 days or 5 half-lives (whichever is longer) before the study treatment administration. • Significant concurrent, uncontrolled medical condition including but not limited to renal, hepatic, hematological, GI, endocrine, pulmonary, neurological, cerebral or psychiatric disease. • History of stroke or intracranial hemorrhage within 6 months of the date of study treatment administration (unless complete and full recovery) • Chronic or current active infections requiring systemic antibiotics, antifungal or antiviral treatment or exposure to live vaccines within 30 days of study treatment. • Known HIV infection.

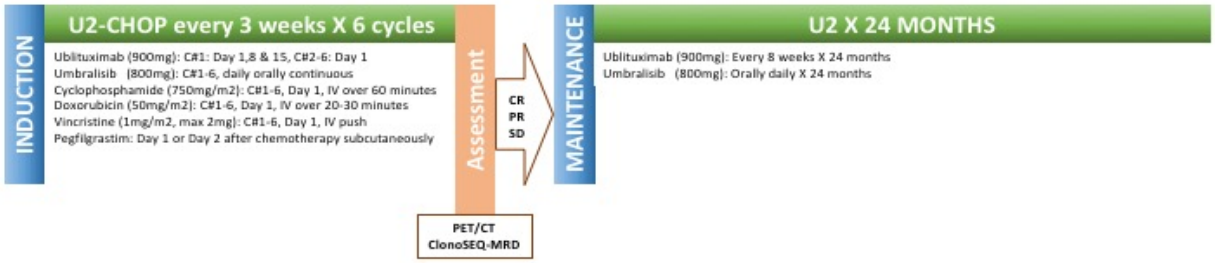
	• Evidence of Hepatitis B or Hepatitis C infection or risk of reactivation. HBV DNA and HCV RNA Evidence of chronic active Hepatitis B (HBV, not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), active cytomegalovirus (CMV), or known history of HIV. If HBc antibody is positive or CMV IgM is reactive the subject must be evaluated for the presence of HBV or CMV DNA (by PCR)
	• 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
	• Any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
	  • Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV)[see Appendix: NYHA Classifications]
	  • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, CHF, or myocardial infarction within 6 months of enrollment.
	  • Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.
	  • Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting within 6 months of enrollment.
	• Cardiac ejection fraction (EF) <45%.
	• Current NY heart association Class II to IV congestive heart failure or uncontrolled arrhythmia
	• Presence of an abnormal ECG that is clinically meaningful. Patients with QTc interval >450 milliseconds are excluded (corrected by Fridericia).
	• Currently pregnant or breast feeding.
	• Unable to swallow and retain oral medication, malabsorption syndrome, disease significantly affecting GI function, total resection of stomach or small bowel,

	ulcerative colitis, symptomatic IBD or complete or partial obstruction. • Anaphylaxis to monoclonal antibody/Rituximab in past. • Any condition that would, in investigator's judgment, interfere with full participation in the study, including administration of study medication/chemotherapy, attending study visits, pose a risk to the patient or interfere with interpretation of study data. • Inability to comprehend or unwilling to sign the ICF. • Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 21 days prior to registration • Contraindication or intolerance to required supportive care medications (neulasta, acyclovir or bactim/dapson/pentamidine/atovaquone) • Females who are pregnant or lactating.
STUDY PROCEDURES	**Phase IB:** Initially, 3 patients will be enrolled in Phase Ib safety lead in with maximum dose of Ublituximab (900mg) and Umbralisib (800mg) with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) for the Cycle#1 of induction. These patients will be followed for 21 days and safety will be reviewed by Safety monitoring committee (SMC). If no one develops Dose Limiting Toxicities (DLT), the trial will expand into phase II portion. If one of three develops DLT, 3 additional patients will be enrolled on same dose level. If none or 1, develops DLT, the trial will expand into phase II portion. If 2 or more patients develop DLT, Umbralisib dose will be lowered to 600mg repeating similar steps per SMC's recommendations. Once the safe dose of Umrbalisib is identified, study will expand into Phase II portion with that identified and SMC approved dose.
	Induction Therapy: **Screening:** Subjects likely to meet eligibility criteria will be offered participation in the study after investigator verifies UAB CTNMO registration. Subjects will sign informed consent prior to any protocol associated procedures. Screening procedures are outlined in Table and will ensure that subject meets all eligibility criteria, obtain disease assessment at base line to allow efficacy assessment, assess baseline toxicity and provide identification sample(s) for MRD assessment at the end of induction treatment. **U2-CHOP induction therapy:** The total duration of induction is total of 6, 3 weekly cycles each. In all cycles, subjects will receive Ublituximab (for C#1: day 1,8 and 15, C#2-6: day 1), Umbralisib (daily continuous, day 1-21),

	CHO (on day 1) and Prednisone (100mg daily from Day 1-5) (Refer to dose adjusting guidelines in table for CHOP) **Response Assessment:** All subjects will have base line PET/CT scan and Response assessment scan 5-6 weeks post C#6. The response will be assessed by PET/CT criteria for Lymphoma (Cheson et al, 2014, Appendix E). **Maintenance Therapy:** Those subjects with objective response (CR, PR and Stable disease (SD)), will initiate maintenance treatment with U2 (Ublituximab and Umbralisib). Ublituximab will be infused every 8 weeks and Umbralisib will be orally daily for 2 years. **Supportive Therapy:** Growth Factor All subjects will receive growth factor during the induction chemotherapy. Peg-filgrastim will be administered either on same day or day#2 of chemotherapy per center's standards. Short acting growth factors are also allowed (starting on Day2-9 of every induction treatment). Prophylaxis: Viral and Pneumocystis Jirovecii prophylaxis will be given all through the treatment (both induction and maintenance phase) Viral Prophylaxis: All patients will receive Ayclovir (400 BID orally daily) or famciclovir (250mg orally twice a day) or Valacyclovir (500mg orally twice or thrice a day) for prophylaxis. PJP Prophylaxis: Bactrim DS Monday, Wednesday and Friday every week or Dapsone (100mg daily orally)/Atovaquone (1500mg orally daily)/Pentamidine (300mg NEB every 4 weeks) per institution standard. G6PD testing should be done in patients going on Bactrim/Dapsone.
Primary Endpoint	Rate of complete remission at the end of induction treatment (U2-CHOP X 6 cycles) per PET/CT assessment criteria for Lymphoma (Cheson et al, 2014)
Secondary Endpoints	• Rate of Overall Response Rate (CR+PR) • Rate of PFS at 3 years • Rate of OS at 3 years

	• Rate of disease control rate (CR+PR+SD) at 3 years • Rate of MRD negativity at the end of induction • PFS and OS of MRD- subjects
Statistical Methods	Phase IB safety study will use 3+3 dose de-escalation design at two dose cohorts assuming the DLT is no more than (≤) 33% in the combination. The sample size in this portion will range from 3-12. We expect that Umbralisib in combination with Ublituximab-CHOP will improve the CRR to 70% comparing to the standard treatment with R-CHOP alone at 40% response rate. Using Single-Stage Phase II design for Testing H0: P ≤ P0 versus H1: P ≥ P1, A sample size of 25 achieves 90% power to detect a difference (P1-P0) of 0.3 using a one-sided binomial test. If the number of responses is 15 or more, the hypothesis that P <= 0.4 is rejected with a target error rate of 0.050 and an actual error rate of 0.034. If the number of responses is 14 or less, the hypothesis that P >= 0.7 is rejected with a target error rate of 0.1 and an actual error rate of 0.098. Thus, a total of 28-37 of patients will be required to both portions of the study.

STUDY SCHEMA



LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	degrees Centigrade
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time (also PTT)
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CR	complete response
CrCl	Creatinine Clearance
CRF	case report form(s)
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
dL	deciliter
DLT	dose-limiting toxicity
DVT	deep venous thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony stimulating factor
h	hour(s)
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
kg	kilogram(s)

LDH	lactate dehydrogenase
mg	milligram(s)
min	minute(s)
mIU	Milli International Units
mL	milliliter(s)
MM	multiple myeloma
mm^2	millimeter(s) squared
mm^3	millimeter cubed
MCL	Mantle Cell Lymphoma
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (oral)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QIU	Qualified Investigator Undertaking Form
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SPEP	serum protein electrophoresis
STD_{10}	severely toxic dose in 10% of animals
TLS	Tumor lysis syndrome
TTP	time to tumor progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
WBC	white blood count

3.0 INTRODUCTION

Mantle cell lymphoma (MCL) is an incurable hematologic malignancy arising from CD5+ antigen naïve pre-germinal center B cells that comprises approximately 6-7% of all adult Non Hodgkin Lymphoma (NHL)[1]. The incidence of MCL increases with age (average age is 68 years) and is more common in males[1,2]. Although some patients with MCL can have indolent course, majority of them pursue an aggressive course. Most patients of MCL presents with non-bulky lymphadenopathy and advanced stage with frequent extra-nodal involvement. In general, MCL pursue an aggressive course with very poor outcome. The median survival reported in various series is between 3-5 years[3].

The MCL is characterized by unique molecular characteristic of over expression of cell cycle regulator protein cyclin D1 (the first event in lymphomagenesis). This over expression is due to the chromosomal translocation of t(11;14) (q13;q32) which juxtaposes cyclin D1 gene, B-cell leukemia/lymphoma (bcl-1), under control of immunoglobulin heavy chain enhancer. Apart from this characteristic molecular feature, other markers such as CD20 and CD5 expression, inactivating p53 mutations and decreased expression of p27 are also evident in MCL. [4]

Apart from common lymphoma indicators (extra-nodal involvement, age, performance status and LDH), Ki-67 proliferation index has proven to be powerful predictor of survival in MCL in post Rituximab era. Mantle Cell International Prognostic Index (MIPI) identified four independent prognostic factors (age, performance status, LDH and WBC count). Based on these prognostic factors, the patients can be classified into high risk (OS of 2 years), intermediate risk (OS of 4 years) and low risk (OS of 6 years). [5 6 7-9]

MCL is still considered incurable with currently available treatment options. MCL has wide spectrum of clinical presentation ranging from indolent disease to symptomatic aggressive disease. Indolent disease usually presents with limited stage disease, low tumor burden, without high risk features and low Ki67 expression and has better overall ourtome.[10-13] Unfortunately, majority of the patients will present with advanced systemic and symptomatic disease and symptomatic disease requiring aggressive induction, consolidative and maintenance treatment depending on their physiological status.

The initial treatment of MCL depends on many disease and patient related factors. Advanced, biologically aggressive (high Ki67 index, p53 mutated and blastoid) disease in a young and fit patient needs aggressive/intense induction, ASCT consolidation and maintenance treatment. While unfit patient usually is offered less intense treatment (R-CHOP, R-B, VR-CAP) followed by maintenance treatment.

Rituximab combined with high dose cytarabine (R-Hyper CVAD or R-DHAP) followed by autologous stem cell transplantation (ASCT) is currently considered standard in treatment of MCL for fit patients[14]. The addition of rituximab to multi-agent chemotherapy backbone has improved response rates and outcomes. [15]In a randomized controlled trial of CHOP vs R-CHOP, addition of rituximab lead to better outcomes.[16]

Over the past decade multiple studies have revealed the role of cytarabine in treatment of MCL. Treatment regimens containing high dose cytarabine are shown to produce better complete response rates and PFS[17-20]. In a phase III trial comparing RCHOP(6 cycles) vs RCHOP(3 cycles) alternating with RDHAP(rituximab, dexamethasone, cytarabine and cisplatin)(3 cycles) followed by autologous transplantation, the R-DHAP arm had better CR rate(25% vs 36%, p=0.012), longer response duration (46 vs. 48 months, p=0.0382) and longer OS(82 mths vs. not reached, p=0.045)[21]. In a phase II trial, R-HyperCVAD (rituximab, cyclophosphamide, doxorubicin, vincristine and dexamethasone) alternating with R-MA (rituximab, methotrexate and cytarabine) was was associated with 97% RR

with 87% CR. Impressively, at 10 years follow up the median OS was not reached with median time to failure of 4.6 years. The regimen was associated with higher toxicity profile.[22] Another phase II study of the same regimen confirmed higher CR rates with good survival rates.[23] Although highly active, R-HyperCVAD is associated with significant treatment related toxicity and interruption in therapy.

For unfit patients or who are ASCT ineligible, the treatment options are limited. Most commonly used chemo-immunotherapy regimens are R-CHOP, BR or VR-CAP. A phase II by European MCL network tested RCHOP against FCR (fludarabine, cyclophosphamide and rituximab) followed by second maintenance randomization between Interferon and rituximab.[24] The median OS at 4 years was significantly in favor of the RCHOP arm (62% vs 47%, p=0.005). In second randomization, rituximab maintenance reduced risk of progression or death by 45 %(68% vs 29%), improved duration of response and OS. [24]

Bendamustine in combination with rituximab have shown promising results in first line and relapse refractory setting. In a randomized phase III trial of BR vs RCHOP, BR showed significant improvement in PFS (35.4vs 22.1months) although there was no statistically significant difference in OS[25]. The combination of bendamustine and rituximab with cytarabine was evaluated in a Phase II study of patients older than 65 who were not eligible for aggressive chemotherapy[26]. Among previously untreated MCL patients, the ORR was 100% and the 2 year PFS was 95%. A phase III double-blind study of ibrutinib in combination with BR versus BR for the treatment of patients with newly diagnosed MCL is currently ongoing (NCT01776840)[27].

Bortezomib, a proteasome inhibitor, inhibits 26S proteasome. By doing so, it inhibits NF-kB pathway making it rationale for activity in MCL. It was approved as a single agent, by US food and drug administration (US FDA) in MCL in relapse refractory setting in December 2006. In the registration phase III trial, newly diagnosed MCL patients, not eligible for aggressive chemotherapy were randomized to receive VR-CAP or RCHOP[28]. At follow-up of 4 years VR-CAP patients had better PFS (24.7 vs 14.4 months, p=<0.001) and median OS at 4 years (64% vs 54%) compared to R-CHOP. Based on this trial, US FDA approved VR-CAP in newly diagnosed MCL patients.

Intensive consolidation chemotherapy and high dose chemotherapy followed by autologous transplantation are usually not recommended for patients who above age 65 or who are unfit for such regimens. In much selected elderly patients however, this may be an acceptable option[29]. Autologous HSCT is now considered a standard consolidation strategy for young and fit patients with MCL. In a prospective study of frontline RCHOP/RDHAP followed by ASCT the 3 year even free survival and overall survival were 84% and 90% respectively but the median overall survival not reached[30]. In this trial, the molecular reemission (MRD negative disease) at 2 years post ASCT was associated with improvement in PFS and OS.

The MD Anderson group published a study of Hyper CVAD induction followed by consolidative autoHSCT which showed fiver year disease free survival of 42% and OS of 77%.[31]In the Nordic MCL-2 phase II trial, 160 MCL patients younger than 66 years were given 6 cycles of rituximab and high-dose cytarabine containing induction regimen followed by BEAM (carmustine, etoposide, cytarabine and melphalan) conditioning regimen and ASCT. The CR rate increased from 56% to 90% after myeloablative chemotherapy stressing the role of intensive consolidation therapy in improving the response rate[17]. In the European MCL Network phase III trial, the response rate after autoHSCT was 97% in the two arms but the rate of molecular remission that is a powerful and independent prognostic factor for the duration of the response rose from 55 to 72% after ASCT (p=0.0116)[21,32].

Maintenance therapy with rituximab may provide extended disease control in patients who are unable to undergo aggressive chemotherapy and/or ASCT. In a pilot phase II study, previously

untreated patients with MCL were treated with modified less intense HyperCVAD followed by rituximab maintenance for 5 years. The median PFS was 37 months and median OS was not reached in favor of rituximab maintenance [33]. In another study of modified HyperCVAD with bortezomib followed by rituximab maintenance, median PFS and OS were not reached at 4 years[34].

Phosphoinositide 3-kinase inhibitors (PI3K inhibitors) are a class of drugs that inhibit the phosphoinositide 3 kinase enzymes which are part of the Pi3K/AKT/mTOR pathway. The phosphatidylinositol-3-kinase pathway is known to have a significant role in B-cell function including B-cell antigen receptor signaling. Inhibition of PI3K delta dependent signaling has been shown to have antitumor effect by inducing apoptosis and affecting the tumor microenvironment. Two class I PI3K isoforms inhibitors have been tested for relapsed MCL, the oral isoform-selective inhibitor PI3K (CAL-101/ GS-1101, idelalisib) that blocks survival signals, induces apoptosis and disrupts signals between the tumor microenvironment and B-cell malignancies[35-37] and the more pleiotropic PI3K- (Copanlisib / BAY 80 – 6946) that exhibits preferential inhibition of AKT phosphorylation, superior antitumor activity and potent apoptosis inducing activity[38]. A phase I trial of Idelalisib, in heavily pretreated patients with MCL confirmed the activity of this compound with an ORR of 40% (5% CR) and a 1-year PFS of 22%[39]. Copanlisib, an intravenous formulations has been evaluated in a phase II study in various lymphomas, including 7 patients with MCL with ORR of 71% (1 uCR / 4 PR)[40].

3.1 UMBRALISIB

Umbralisib is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The PI3Ks are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies.

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

Preclinical Evaulations 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.

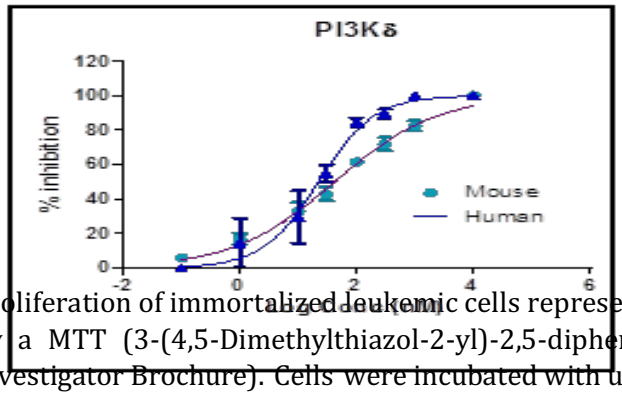


FIGURE 1: UMBRALISIB POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

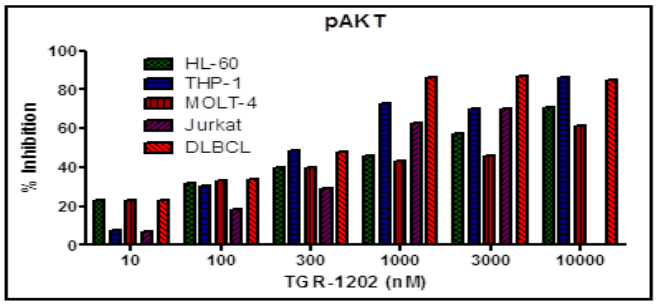
PI3K isoforms (Human)	IC_{50} (nM)
A	>10,000
B	1,116
Γ	1,065
Δ	22.23

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

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

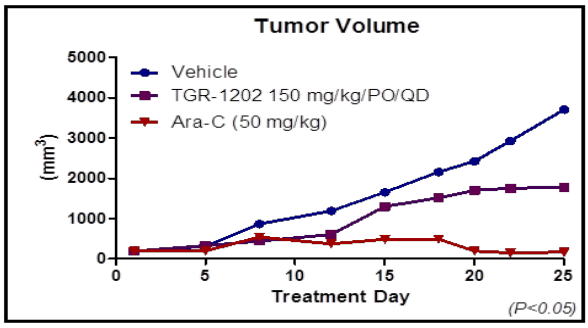
Subsequent to cell viability, the effect of umbralisib on AKT phosphorylation (Umbralisib Investigator Brochure) was determined. AKT, a serine threonine kinase mediates the downstream effects of PI3K activity and modulates several cell processes including survival and growth. Reduction of phosphorylated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

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



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



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.

CLINICAL DEVELOPMENT OF UMBRALISIB

Single-Agent in Patients with Relapsed or Refractory Hematologic Malignancies

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

Patients have been enrolled in a 3+3 dose-escalation design starting at 50 mg QD with subsequent cohorts evaluating doses as high as 1800 mg QD. In an effort to further improve the oral bioavailability of umbralisib, the particle size of the drug product was reduced through a micronization process, resulting in greater absorption when tested in a bioequivalence crossover study in healthy subjects . This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1200 mg QD, with no maximum tolerated dose (MTD) reached. Intra-patient dose escalation rules have allowed patients enrolled into the study in early cohorts to increase their dose of umbralisib as subsequent higher cohorts have cleared safety evaluation.

A dose-dependent response has been observed with umbralisib, with a dose of 800 mg or higher of the initial formulation or any dose of the micronized formulation producing significant nodal

reductions among CLL patients. Of the 17 evaluable CLL patients treated at or above this therapeutic threshold, 16/17 (94%) have achieved a nodal partial response, and nodal reductions show an improvement with time on umbralisib with a median time on study of 6 months. Clinical activity was also observed in FL, with 12/16 (75%) evaluable patients experiencing tumor reductions, and a preliminary 38% ORR (6/16) with an additional 2 patients achieving 49% reductions in tumor burdens (patients continuing to receive ongoing therapy).

In all treated patients (81), the most commonly-occurring (≥18% patients) adverse events (AEs; all grades, all causality) were nausea, diarrhea, fatigue, rash, headache, cough and vomiting, the majority of which were Grade 1/2. The only Grade ≥3 AE occurring in >10% of patients was neutropenia (11%). No events of colitis have been observed. Discontinuation due to an AE was reported in only 6/81 (7%) of patients. Less commonly-occurring AEs (9-12%) included constipation, decreased appetite, hypokalemia, anemia, dizziness, dyspnea, pyrexia, abdominal pain, arthralgia and insomnia. Dosing of umbralisib initially occurred in the fasting state, but was transitioned mid-study to fed state dosing, with patients instructed to take umbralisib with food. All dosing of umbralisib is now conducted using the micronized formulation and in the fed state.

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

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.

TGR-1202-PK101: Food Effect

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

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

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

Food increased both the extent and rate of exposure of umbralisib. The extent (AUC_{0-t}) and total extent (AUC_{0-inf}) of exposure increased by 61% and 67%, respectively, when umbralisib was

administered under fed conditions compared to fasting conditions. The peak plasma levels of umbralisib increased by over 173% when umbralisib was administered with food.

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

TGR-1202-PK102: Formulation Effect

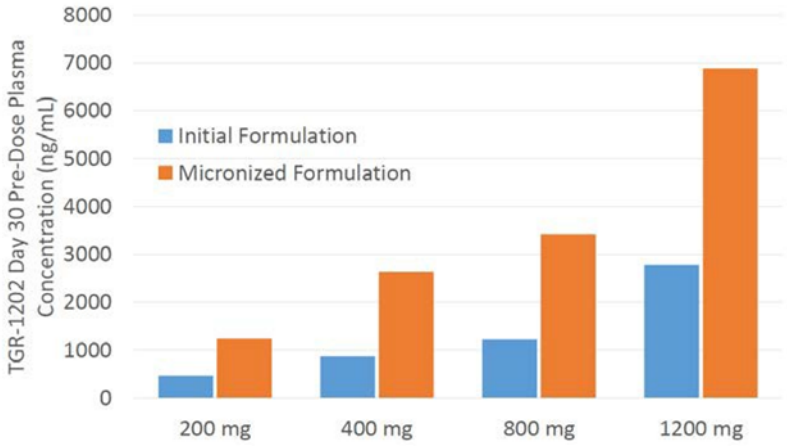
Study TGR-1202-PK 102 was a two-period, randomized, two-way cross over, relative bioavailability and pharmacokinetic bioequivalence study with two different drug product formulations of umbralisib. In this study, umbralisib was administered under fasted conditions in 24 healthy subjects (12 males and 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 Formulatio	Micronized Formulatio		
$AUC_{0\text{-}t}$ (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95
$AUC_{0\text{-}inf}$ (ng·hr/mL)	7715.67	12378.19	160.43	146.49 – 175.70
C_{max} (ng/mL)	166.20	371.70	223.65	202.33 – 247.20

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

Using these mean values, a 320 mg oral dose of umbralisib in the original formulation under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of the original formulation umbralisib under fasted conditions in term of exposure based on $AUC_{0\text{-}inf}$.

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



3.2 UBLITUXIMAB

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

Pre-Clinical Development Of Ublituximab

In-Vitro Activity

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

In Vivo Activity

The antitumor effect of ublituximab was compared to that of rituximab with chemotherapy in follicular lymphoma (FL), and mantle cell lymphoma (MCL) xenograft murine models. Single agent ublituximab demonstrated dose-related anti-tumor activity with 100% tumor growth inhibition in the FL xenograft at a dose of 100mg/kg, and a superior tumor growth delay (21 days) compared to rituximab. Ublituximab also demonstrated superior anti-tumor activity compared to rituximab against MCL xenografts at all dose levels (Esteves IT, 2011).

Toxicology

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

Clinical Development of Ublituximab

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

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

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

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

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

Of the 8 CLL patients enrolled, 4 had infusion related reactions that were manageable with infusion

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

Pharmacokinetics

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

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

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

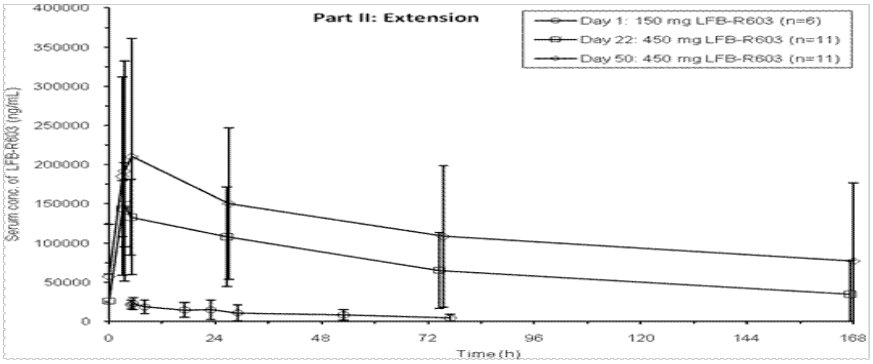


TABLE 1: PHARMACOKINETIC RESULTS AFTER THE 1ST (150 MG), THE 4TH (450 MG) AND THE 8TH (450 MG) INFUSION OF UBLITUXIMAB

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

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

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

Ublituximab in Combination with TGR-1202

The combination of ublituximab and TGR-1202 is currently under evaluation in registration trials in CLL and various B cell NHL histologies. Preliminary results of an ongoing Phase I/Ib study in patients with relapsed or refractory NHL and CLL have been reported (Lunning et al., 2015). In early cohorts, patients received ublituximab on days 1, 8 and 15 of Cycles 1 & 2, then on day 1 of Cycles 4, 6, 9, and 12. In later cohorts, the ublituximab administration schedule was amended to infusions on days 1, 8, and 15 of Cycle 1, followed by Day 1 of Cycles 2 through 6. CLL patients receive Cycle 1, Day 1 infusions split over Days 1 and 2. TGR-1202 is taken once daily until patients are removed from study as per the protocol.

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

Cohort	Ublituximab NHL Dose	Ublituximab CLL Dose	TGR -1202 Dose (QD)
1	900 mg	600 mg	800 mg
2	900 mg	600 mg	1200 mg
3	900 mg	900 mg	400 mg (micronized)
4	900 mg	900 mg	600 mg (micronized)
5	900 mg	900 mg	800 mg (micronized)
6	900 mg	900 mg	1200 mg (micronized)

As of December 1, 2015, 71 patients have been enrolled and are evaluable for safety, with 58 patients evaluable for efficacy. The median age was 65 years (range 26 – 86), 47 Male/24 Female, with histologies as follows: 24 DLBCL, 19 CLL/SLL, 19 FL, 6 MZL, 2 MCL, and 1 patient with Richter's Transformation. Patients had a median of 3 prior therapies, and 58% were refractory to prior therapy.
Among the 71 patients evaluable for safety, nausea was the most prevalent adverse event (46%), followed by diarrhea (44%), fatigue (41%), neutropenia (30%), and infusion related reaction (25%). Seven patients had their dose of TGR-1202 reduced due to various adverse events. IRR and neutropenia were managed through dose delays, with 1 CLL patient having a neutropenia related dose delay which met the criteria for a DLT, necessitating enrollment of additional CLL patients into Cohort 1. Overall 8% of patients have discontinued TGR-1202 due to an adverse event.
Sixteen DLBCL patients treated with ublituximab + TGR-1202 were treated with therapeutic doses, amongst whom, the overall response rate was 31% with three patients experiencing a complete remission as confirmed by independent review. Amongst the five patients who responded, three had GCB subtype, while the other two patients subtype was not known.

Overall, the preliminary data suggests the combination of ublituximab and TGR-1202 is well tolerated and active in patients with relapsed or refractory hematologic malignancies, including those with DLBCL.

Minimal Residual Disease in MCL

The most frequently used methods for monitoring treatment response in lymphoma is PET and CT imaging. However, both these modalities have limitation of detecting disease at micro levels. Minimal residual disease (MRD) assessments in MCL by various methods have been explored but allel specific quantitative polymerase chain reaction method have been very sensitive and specific. Compared to other MRD detection methods (flow cytometry, PCR) the clonoSEQ assay is 10-100x more sensitive. The assay has the capability of identifying one cancer in one million healthy cells (Sala Torra et al 2017). This assay has undergone clinical validation and fulfills the requirements for regulatory review. It uses next generation DNA sequencing (NGS) and can serve as a standardized way to determine treatment effect. Panel directed NGS MRD detection uses the

genetic features of lymphoma to identify tumor specific DNA in the patient's blood. (https://www.adaptivebiotech.com/)

MRD assessment in MCL has been prognostic as well as can be used as surrogate for efficacy of the induction treatment. Here in this study, our exploratory objective is to assess the rates of MRD negativity at the end of the induction treatmnet (after C#6 of U2-CHOP).

3.3 Rationale for this Study

MCL majoritily, is an aggressive and incurable lymphoma. As it is the lymphoma of elderly, aggressive treatment approaches like aggressive induction treatments and ASCT may be more risky in this population. Majority of these patients are treated with less intense approach like Rituximab-Bendamustine (BR), R-CHOP or VR-CAP. Nearly all the patients are treated with Rituximab maintenance after these induction approaches.

In this proposal, we want to explore combination of novel CD20 monoclonal antibody (Ublituximab) with CHOP and a novel highly active PI3K inhibitor (Umbralisib) in ASCT ineligible untreated advanced MCL. Ublituximab, a novel third generation chimeric anti-CD20 monoclonal antibody with a low fucose content, has potential to induce superior antibody-dependent cytotoxicity (ADCC). Ublituximab exhibits competitive complement-dependent cytotoxicity (CDC), on par with rituximab, and has also been demonstrated to induce programmed cell death (PCD) upon binding to the CD20 antigen on B-lymphocytes. Umbralisib is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. Umbralisib is highly active in various B cell lymphomas. The combination of Ublituximab and Umbralisib is being evaluated in two signature clinical trials. The preliminary data suggests that the combination is safe and well tolerated.

To improve upon the back bone of R-CHOP, we want to exlore U2-CHOP (Ublituximab with Umbralixib)-CHOP followed by U2 maintnenance in ASCT in eligible patients. Both the study agents (U2) are highly active in lymphomas. Our hypothesis is to improve rates of complete response at the end of induction treatment with this novel combination. We also want to explore if this novel combination induces more MRD negativity (as exploratory objective).

4.0 OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

Phase Ib:

- To determine the safety of Umbralisib and Ublituximab in combination with CHOP chemotherapy for newly diagnosed MCL

Phase II:

- CRR: To determine the efficacy of U2-CHOP in terms of Complete Response rates (CRR) in patients with untreated MCL after induction phase (6 cycles of U2-CHOP) by PET/CT response assessment criteria by Cheson 2014 (appendix)

4.2 Secondary Objectives

Phase II:

- To determine Overall response rate (ORR=CR+PR) of the induction treatment with U2-CHOP in untreated MCL
- To determine Overall Survival (OS) at 3 years
- To determine Progression Free Survival (PFS) at 3 years
- To determine the rate of disease control (CR+PR+SD) at 3 years

4.3 Exploratory Objective:

- To determine the frequency of MRD negative (MRD-) disease at the end of induction treatment with U2-CHOP.

4.4 Efficacy Endpoints

Primary Endpoint:

- Rate of complete remission at the end of induction treatment (U2-CHOP X 6 cycles) per PET/CT assessment criteria for Lymphoma (Cheson et al, 2014)

Secondary Endpoints:

- Rate of Overall Response Rate (CR+PR)
- Rate of PFS at 3 years
- Rate of OS at 3 years
- Rate of disease control rate (CR+PR+SD) at 3 years
- Rate of MRD negativity at the end of induction
- PFS and OS of MRD- subjects

5.0 ELIGIBILITY CRITERIA

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

5.1 Inclusion Criteria

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

- Males or female patients $\geq$18 years of age
- Diagnosis if MCL (Stage II, III, IV) as supported by histology and over expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) by FISH (fluorescent in situ hybridization) with indication of initiation of therapy.
- At least one LN of >1.5 cm size as index/measurable site of disease

- No prior therapy for MCL
- Not eligible for bone marrow transplantation (assessed by treating physician due to comorbidities) or not interested in bone marrow transplant (clear documentation of patient's unwillingness to pursue transplant)
- Eastern cooperative Oncology Group (ECOG): 0,1 or 2 (Appendix)
- Absolute neutrophil count (ANC) ≥1500 (≥1000 if bone marrow involvement with MCL) within 28 days prior to initiation of therapy
- Platelets ≥100000 cells/μL (≥75000 cells/μL if bone marrow involvement with MCL) within 28 days prior to initiation of therapy
- Hemoglobin ≥9.0 gm/dL (≥8.0 gm/dL if bone marrow involvement with MCL) within 28 days prior to initiation of therapy
- Alanine transaminase (ALT)/Aspartate Transaminase (AST) <3.0 X Upper limit of Normal (ULN) within 28 days prior to initiation of therapy
- Total Bilirubin <2 X ULN within 28 days prior to initiation of therapy
- Calculated Creatinine Clearance ≥35 mL/min by Cockcroft-Gault Equation
- Male patients must agree to use an acceptable method of contraception for the entire duration of study.
- All patients (or their legal representative) must have signed an informed consent indicating that they are willing to participate in the study and are willing to follow the procedure required by the study in accordance with federal, local and institutional guidelines.
- Female patients who are not of child-bearing potential (see Appendix: CONTRACEPTION GUIDELINES AND PREGNANCY), and female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of either study drug.

5.2 Exclusion Criteria

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

- Any prior anti-neoplastic therapy for MCL
- CNS involvement by MCL
- Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or localized thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas.
- If patient has received prior anthracycline therapy, the cumulative anthracycline dose should be <150mg/m2 of doxorubicin equivalent
- H/O prior Allogeneic transplantation or autologous stem cell transplantation for any other reason.
- Use of immunosuppressive therapy (e.g. cyclosporine A, tacrolimus or high dose steroids). Patients receiving steroids must be at a dose of <10mg/day prednisone (or equivalent) within 7 days of the first day of the study treatment administration. Patients are allowed to use topical or inhaled corticosteroids.

- Concurrent any anticancer therapy for any other cancer (chemotherapy, radiation, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy or tumor embolization).
- Use or expected use during the study of any prohibited medications including potent CYP3A4 inhibitors, inducers, substrates (appendix) within 14 days or 5 half-lives (whichever is longer) before the study treatment administration.
- Significant concurrent, uncontrolled medical condition including but not limited to renal, hepatic, hematological, GI, endocrine, pulmonary, neurological, cerebral or psychiatric disease.
- History of stroke or intracranial hemorrhage within 6 months of the date of study treatment administration (unless complete and full recovery)
- Chronic or current active infections requiring systemic antibiotics, antifungal or antiviral treatment or exposure to live vaccines within 30 days of study treatment.
- Known HIV infection.
- Evidence of Hepatitis B or Hepatitis C infection or risk of reactivation. HBV DNA and HCV RNA 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 or CMV IgM is reactive the subject must be evaluated for the presence of HBV or CMV DNA (by PCR)
- 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
- Any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
    - Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV)[see Appendix: NYHA Classifications]
    - Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, CHF, or myocardial infarction within 6 months of enrollment.
    - Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.
    - Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting within 6 months of enrollment.
- Cardiac ejection fraction (EF) <45%.
- Current NY heart association Class II to IV congestive heart failure or uncontrolled arrhythmia
- Presence of an abnormal ECG that is clinically meaningful. Patients with QTc interval >450 milliseconds are excluded (corrected by Fridericia).
- Currently pregnant or breast feeding.
- Unable to swallow and retain oral medication, malabsorption syndrome, disease significantly affecting GI function, total resection of stomach or small bowel, ulcerative colitis, symptomatic IBD or complete or partial obstruction.
- Anaphylaxis to monoclonal antibody/Rituximab in past.

- Any condition that would, in investigator's judgment, interfere with full participation in the study, including administration of study medication/chemotherapy, attending study visits, pose a risk to the patient or interfere with interpretation of study data.
- Inability to comprehend or unwilling to sign the ICF.
- Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 21 days prior to registration
- Contraindication or intolerance to required supportive care medications (neulasta, acyclovir or bactim/dapson/pentamidine/atovaquone)
- Females who are pregnant or lactating.

5.3 Subject Enrolment

Once a patient is identified as a candidate for the trial the investigator will contact the UAB CTNMO registration office (205-975-5387, Fax No: 205-975-9875) prior to obtaining informed consent (safety lead in cohort only). This process is intended to verify if a "slot" is available in the current cohort. Registration will be completed upon submission of documentation of eligibility to the registration office and issuance of a registration confirmation email.

Prior to accepting the registration, the registration office will verify the following:

- IRB approval at the registering institution.
- Patient eligibility.
- Existence of a signed consent form.
- Existence of a signed authorization for use and disclosure of protected health Information.
- Pretreatment tests and procedures must be completed within the guidelines specified in the test schedule, including assessment of baseline symptoms.
- Study drugs availability on site (for initial site patient only; Local site is responsible for assessing drug available for subsequent site enrollments).

6.0 TREATMENT AND PROCEDURES:

This is a single arm, multi-center, open label Phase II trial with safety lead in Phase Ib.Treatment will be administered on an outpatient basis in 3-week (21 day) cycles.

6.1 Phase Ib:

In phase Ib portion, 3 patients will be enrolled at the following dose levels of the induction treatment. These patients will be followed for 21 days to assess the Dose Limiting Toxicities. If no DLT occurred, the study will expand to phase II portion. If 1 DLT occurred (in 21 days), additional 3 patients will be evaluated; if $\leq$1 DLT occurred in these three new patients, the study will expand to phase II portion. If $\geq$2 DLT in these three new patients, the dose will be reduced to the lower dose cohort: 3 patients will be evaluated at lower dose (600mg), if no DLT occurred, the study will expand to phase II portion; if 1 DLT occurred (in 21 days), additional 3 patients will be evaluated; if $\leq$1 DLT occurred in these three new patients, the study will expand to phase II portion; if >=2 DLT in these three new patients, the safety monitoring committee will gather to decide lower dose and planning of further cohort.

6.2 Dose Limiting Toxicities:

- DLT will be evaluated in Phase Ib portion from the beginning of the treatment to 21 days
- DLTs are defined as any of the following in the DLT-evaluation period, graded according to the National Cancer Institute's common Terminology Criteria for Adverse Events INCI CTCAE), version 4.03(Appendix):

- Grade 3 non-hematologic lab abnormality
- ≥ Grade 4 neutropenia lasting more than 10 days
- ≥ Grade 3 Febrile Neutropenia
- ≥ Grade 4 thrombocytopenia (< 25,000/mm^3) lasting for more than 10 days
- ≥ Grade 4 anemia unrelated to the disease
- Delay of C#2 more than 7 days due to toxicities
- ≥ Grade 4 tumor lysis syndrome
- ≥Grade 3 transaminitis
- Any life-threatening infection (viral, bacterial or fungal) leading to death
- Death related to study agent
- Any non-hematologic AE ≥ Grade 3 (fever, chills, dyspnea, rash, fatigue, flu-like syndrome, pain, anorexia, glucose intolerance, alkaline phosphatase elevation or hypertension)

6.3 Induction treatment: (Phase I and II)

Treatment	Age <70	Age>70
Ublituximab IV	900mg	900mg
Umbralisib Orally (once a day)	800mg	800mg
Cyclophosphamide IV	750mg/m2	500-750mg/m2*
Doxorubicin IV	50mg/m2	25-50mg/m2*
Vincristine IV	1mg/m2 (max 2mg)	1mg/m2 (max 2mg) *
Prednisone Orally (Day 1-5)	50-100mg	50-100mg

*Dose adjustments are allowed on CHOP treatment based on investigators assessment for elderly patients. Elderly patients (>70 years) may not tolerate full dose CHOP treatment so 25% dose reductions on CHOP treatments are allowed.

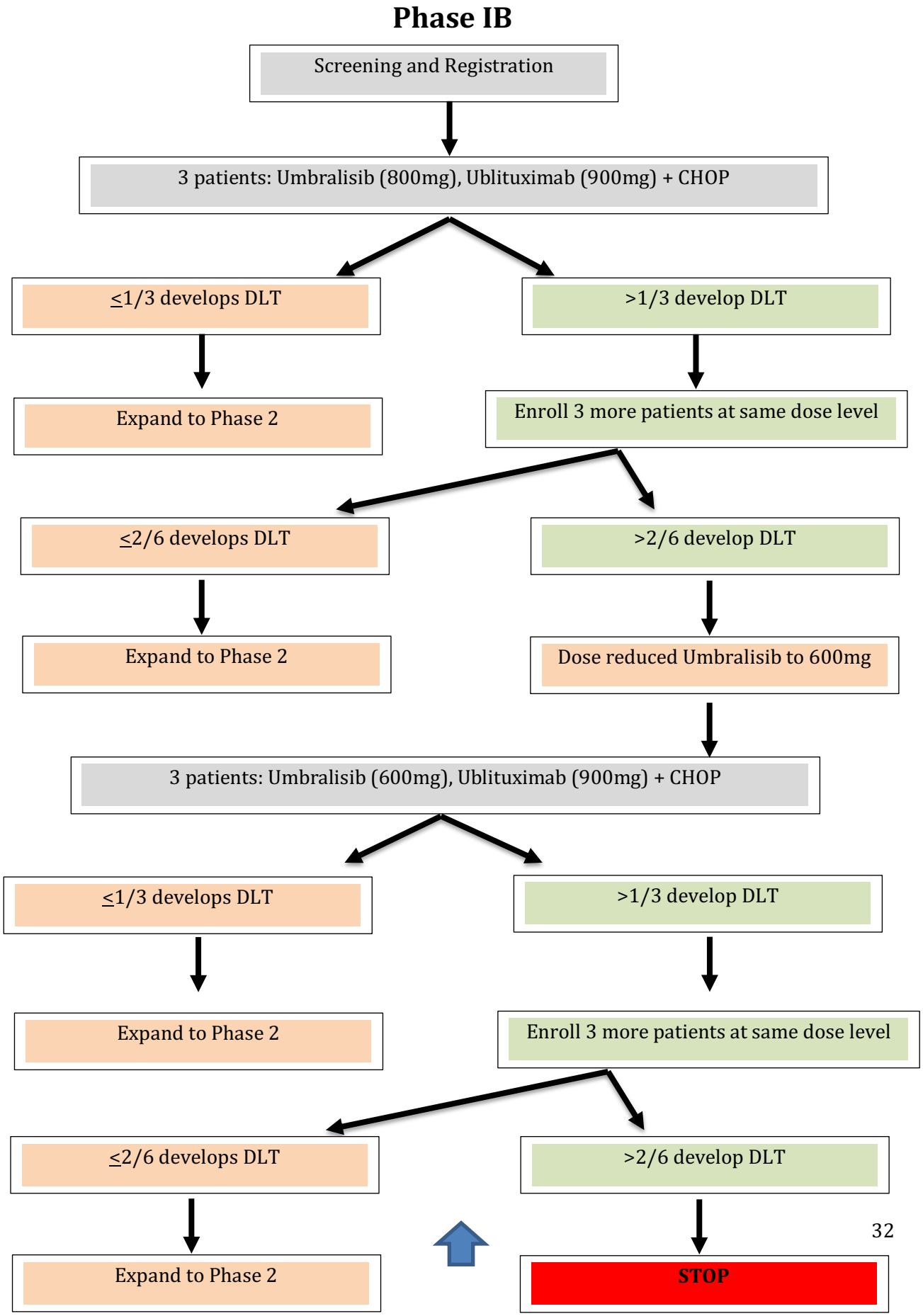
6.4 Phase II:

- Once Umbralisib dose is defined in phase Ib, the study will expand to phase II portion after SMC/DSMB (Safety monitoring committee/Data Safety Monitoring Committee) agrees.
- The induction treatment will be as outlined above in the table for 6, 3 weekly cycles

6.5 Maintenance Treatment:

- Maintenance treatment will start 8 weeks after C#6.
- Ublitixumab will be given IV every 8 weeks for 24 months
- Umbralisib will be given orally daily for 24 months
- Throughout the study duration (both induction and maintenance phase), viral and PJP prophylaxis will be continued
- Peg-filgrastim is allowed considered in maintenance phase in case of neutropenia
- Umbralisib dose reduction may be allowed after discussing with sponsor.

Figure: 2 (Phase Ib portion outline)



7.0 AGENT ADMINISTRATION AND DOSING GUIDELINES

7.1 Guidelines for Administration of Umbralisib

- *Method of Administration:* Umbralisib will be administered orally once daily with food.
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:* Patients are required to start prophylaxis treatment for pneumocystis jiroveci pneumonia (PCP) as well as antiviral therapy prior to Cycle 1 Day 1.
    - *Anti-viral Prophylaxis*: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent
    - *PCP Prophylaxis:* Bactrim DS 1 tablet 3x per week or Dapsone 100 mg daily or equivalent
- Final choice of PCP and anti-viral prophylaxis therapy is per investigator discretion.

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. Patients should be instructed to return all empty and partially filled bottles including any unused tablets when they return to the site. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle and as needed.

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

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

Dispensing of Umbralisib

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

7.2 Guidelines for Administration of Ublituximab

- *Method of Administration:* Ublituximab will be administered as an intravenous infusion through a dedicated line.
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:* Pre-medicate approximately 30 minutes prior to each dose of ublituximab with an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent).
    - Use of oral acetaminophen 650 mg (or equivalent) should be restricted to patients who experience fever or pyrexia after week 1 dose, or as clinically warranted.
    - After cycle 6, if use of a corticosteroid is of clinical concern, please contact the Principal Investigator.

- *Hypersensitivity and Infusion Reaction Precautions*: Medication and resuscitation equipment must be available per institutional guidelines prior to ublituximab administration for the emergency management of potential anaphylactic reactions.
- *Patient Care Implications*:
    - Ublituximab should not be administered as an IV push or bolus.
    - Ublituximab may be administered on an outpatient basis.
    - Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab should not be administered if does not conform to the specifications. Immediately inform TG Therapeutics with any product quality concerns or questions.
    - It is recommended that ublituximab be administered immediately after dilution.
    - No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).
    - Concurrent glucocorticoid therapy as long as started for at least 7 days prior to study entry (≤ 10 mg per day of prednisone or equivalent) is allowed as clinically warranted.
    - Since infusion-related hypotension may occur, **antihypertensive medications should be withheld 24 hours prior to and throughout infusion of ublituximab.**
    - For patients at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

Infusion Related Reactions and Infusion Rate Guidance – Ublituximab

Infusion related reactions including severe reactions have been reported with ublituximab administration. Guidelines are provided below for patients who experience such reactions. Symptomatic infusion reactions, despite premedication, may be treated at the discretion of the treating physician, including but not limited to: oral acetaminophen 650 mg (or equivalent), corticosteroids, antihistamines, oxygen, and bronchodilators.
The following are recommended infusion rate reduction/delay guidelines for patients who experience severe Infusion Related Reactions (IRR's) that result in treatment interruption. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator.

1st or 2nd Infusion Interruption:

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

3rd Infusion Interruption (same day):

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

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

Dilutions of Ublituximab

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

Ublituximab is available in 150 mg single use vials as a 25 mg/mL concentrate for dilution (6 mL quantity vial).

Dosing Delays and Modifications

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

Dose Delay/Modifications: Umbralisib

Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. A maximum 28-day (1 cycle) delay for recovery from toxicity is allowed for umbralisib to allow recovery of hematologic toxicities to ≤ Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If the patient withdraws consent or has documented progression, an end of study visit should be completed.

TABLE 3: UMBRALISIB DOSE DELAY AND/OR MODIFICATIONS GUIDANCE

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 2 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 3 neutropenia	Maintain current dose, consider supportive care. If recurrence or persistent Grade 3, resume at next lower dose level at discretion of the investigator.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay umbralisib until Grade ≤3 and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider supportive care. If delay is > 28 days discontinue study drug. If recurrence after re-challenge, resume at next lower dose level at discretion of the investigator.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose level and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay umbralisib until Grade ≤3; thereafter, resume at full dose. Consider supportive care intervention as warranted. If delay is > 28 days, discontinue umbralisib.

	If recurrence after re-challenge, resume at next lower dose level at discretion of the investigator.
Pulmonary & Related Infections*	
Grade 2	Stop all therapy and hold until resolution. Restart umbralisib at current dose or one lower dose level per PI discretion. Restart ublituximab at full dose. If recurrence after re-challenge, resume at next lower dose level at discretion of the investigator.
Grade ≥3	Stop all therapy and hold until resolution. Restart umbralisib at one lower dose level per PI discretion.
***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.**	
All Other Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level. NOTE: If persistent grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ grade 1. If recurrence after re-challenge, resume at full dose or next lower dose level at discretion of the investigator.
Grade ≥3	Withhold umbralisib until Grade ≤2. If recurrence after re-challenge, resume at full dose or next lower dose level at discretion of the investigator.
Diarrhea and/or Colitis	
Diarrhea Grade ≤2	Maintain current dose level if tolerable or hold and then resume at current dose level once has resolved. **NOTE**: If persistent grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ grade 1. If recurrence after rechallenge, resume at full dose or next lower dose level at discretion of the investigator.
Diarrhea Grade ≥3	Withhold umbralisib until Grade ≤2. Resume at full dose or next lower dose level as per discretion of investigator If recurrence after rechallenge, resume at next lower dose level at discretion of the investigator.
Colitis (all Grades)	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level

STUDY DRUG DOSE REDUCTION RECOMMENDATIONS

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

A maximum of two dose level reductions are allowed for umbralisib.

If a 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.

Dose Delay/Modifications: Ublituximab

No reduction in the dose of ublituximab is permitted.
Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. A maximum 28 day delay of the next scheduled ublituximab dose is allowed for recovery of hematologic toxicities to ≤ Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If the patient withdraws consent or has documented progression, an end of study visit should be completed.

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

TABLE 4: UBLITUXIMAB DOSE DELAY AND/OR MODIFICATIONS GUIDANCE

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 3 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay ublituximab until Grade ≤ 3 and/or neutropenic fever or infection is resolved; consider growth-factor support as warranted; thereafter, resume at full dose. If delay is > 28 days, discontinue ublituximab.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay ublituximab until Grade ≤ 3; consider intervention with supportive care as warranted; thereafter resume at full dose. If delay is > 28 days, discontinue ublituximab.
Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose.
Grade ≥3	Withhold ublituximab until Grade ≤ 2 at the discretion of the investigator; consider supportive care intervention as warranted. Resume at full dose or if delay > 28 days, discontinue ublituximab.

Ordering Ublituximab and Umbralisib

Ublituximab and TGR-1202 (umbralisib) are available from TG Therapeutics. Please contact Hari Miskin at hm@tgtxinc.com and Peter Sportelli at ps@tgtxinc.com to order. Please allow 5 to 7 business days between drug ordering and drug arrival.

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

STUDY MEDICATION OVERVIEW AND SAFETY

Umbralisib (TGR-1202)

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

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

Availability: Umbralisib is available from TG Therapeutics.

COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in patients treated with single agent umbralisib and were considered at least possibly related to study medication. See the umbralisib investigator brochure for a complete list of all adverse events reported regardless of causality.

Common (>20%)

- **Gastrointestinal disorders**: Nausea, Diarrhea
- **General disorders and administration site conditions:** Fatigue

Less Common (≥10% - ≤20%)

- **Blood and lymphatic system disorders:** Neutropenia
- **Gastrointestinal disorders**: Vomiting
- **Metabolism and nutrition disorders**: Decreased appetite
- **Skin and Subcutaneous Tissue Disorders:** Rash

Uncommon (≥1% - <10%)

- **Blood and lymphatic system disorders:** Anaemia, Febrile neutropenia, Leukocytosis, Thrombocytopenia
- **Eye disorders**: Vision blurred
- **Gastrointestinal disorders:** Abdominal distension, Abdominal pain, Constipation, Dry mouth, Dyspepsia, Colitis
- **General disorders and administration site conditions:** Asthenia, Chills, Oedema peripheral, Pyrexia,
- **Infections and infestations:** Oral candidiasis, Pneumonia, Upper respiratory tract infection
- **Investigations:** Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Lymphocyte count increased, Weight decreased
- **Metabolism and nutrition disorders:** Dehydration, Hyperglycaemia, Hypokalaemia, Hypophosphataemia,
- **Musculoskeletal and connection tissue disorders:** Arthralgia, Muscle spasms, Pain in extremity
- **Nervous system disorders:** Dizziness, Dysgeusia, Headache, Neuropathy peripheral, Tremor
- **Psychiatric disorders:** Insomnia
- **Respiratory, thoracic and mediastinal disorders:** Cough
- **Skin and subcutaneous tissue disorders:** Alopecia, Night sweats, Pruritus

Events Reported in Less Than 1% of Subjects

- **Blood and Lymphatic System Disorders**: Leukopenia, Hyperbilirubinemia, Bacteremia
- **Ear and Labyrinth Disorders**: Tinnitus
- **Eye Disorders**: Visual Impairment, Visual acuity reduced
- **Gastrointestinal Disorders**: Eructation, Flatulence, Gastrooesophageal Reflux Disease, Abdominal Pain Upper, Mouth Ulceration, Anal Hemorrhage, Hypoaesthesia Oral, Paraesthesia Oral, Pancreatitis, Ileus
- **General Disorders and Administration Site Conditions**: Malaise, Mucosal Inflammation,

- **Hepatobiliary Disorders**: Hypocalcemia
- **Immune System Disorders:** Allergic reaction
- **Infections and Infestations**: Candida infection, Fungal skin infection, Lung infection, Sinusitis
- **Investigations**: International Normalized Ratio Increase, Blood lactate dehydrogenase increase, Blood phosphorus increased, Blood sodium increased, Blood uric acid increased, White blood cell count decreased
- **Injury, Poisoning and Procedural Complications**: Contusion
- **Metabolism and Nutrition Disorders**: Hyperlipidemia, Hypertriglyceridemia, Hyponatremia
- **Musculoskeletal and Connective Tissue Disorders**: Muscular Weakness, Myalgia, Pain in Jaw
- **Nervous System Disorders**: Somnolence, Peripheral Sensory Neuropathy, Memory Impairment
- **Psychiatric Disorders**: Anxiety, Libido Decrease, Delirium, Parasomnia
- **Reproductive System and Breast Disorders**: Erectile Dysfunction
- **Respiratory, Thoracic and Mediastinal Disorders**: Dyspnea, Epistaxis, Hypoxia, Influenza, Respiratory Failure, Pulmonary edema
- **Skin and Subcutaneous Tissue Disorders**: Dermatitis, Dermatitis Acneiform
- **Vascular Disorders**: Hot Flush

Ublituximab

Chemical Name:	ublituximab
Other Names:	TG-1101
Classification:	Recombinant chimeric anti-CD20 monoclonal antibody
Mode of Action:	Targets CD20 antigen on B-cells
Description:	Ublituximab is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen found on the surface of B lymphocytes. Ublituximab displays the typical structure of immunoglobulins, consisting of two gamma (γ) heavy chains and two kappa (κ) light chains linked by disulfide bridges. It is composed of a murine variable region (37.2% of total amino acids) fused onto human constant regions.
How Supplied:	Concentration of 25mg/mL in 6 mL (150 mg) single-use glass vials.
Storage:	Ublituximab must be stored in a secured, limited-access, refrigerated area at a temperature ranging from +2°C / + 8°C. Ublituximab must not be frozen.
Stability:	Once a vial of ublituximab has been opened and/or diluted it must be used immediately. After dilution, ublituximab is stable in static conditions for 24 hours at 25°C, and in dynamic conditions it is stable for 8 hours at 25°C. Ublituximab has a shelf-life of 36 months if stored between +2°C / + 8°C, based on stability data.
Route of Administration:	Intravenous
Packaging:	Ublituximab is packed in kits. Each kit contains: • Six vials containing 150 mg solution of ublituximab in each or • One vial containing 150 mg solution of ublituximab (for replacement if needed)

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

Availability: Ublituximab is available from TG Therapeutics.

COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in patients treated with single agent ublituximab and were considered at least possibly related to study medication. See the ublituximab investigator brochure for a complete list of all adverse events reported regardless of causality.

Common (>20%)

- **Blood and lymphatic system disorders:** Neutropenia, Thrombocytopenia
- **General disorders and administration site conditions:** Infusion-related reaction, Pyrexia, Chills
- **Nervous system disorders:** Headache

Less Common (≥10 - ≤20%)

- **Blood and lymphatic system disorders:** Anaemia
- **Gastrointestinal disorders:** Diarrhoea, Nausea, Abdominal pain upper
- **General disorders and administration site conditions:** Fatigue, Asthenia

Uncommon (≥5% - < 10%)

- **Blood and lymphatic system disorders:** Febrile neutropenia, Pancytopenia
- **General disorders and administration site conditions:** Pain
- **Infections and infestation:** Bronchitis
- **Investigations:** Blood bilirubin increase, Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Elevated liver enzymes
- **Musculoskeletal and connective tissue disorders:** Muscle weakness
- **Nervous system disorders:** Dysgeusia
- **Respiratory, thoracic and mediastinal disorders:** Throat irritation/tightness, Dyspnea
- **Skin and subcutaneous tissue disorders:** Pruritus
- **Vascular disorders:** Hypertension

Events Reported in at Least One Subject

- **Blood and Lymphatic System Disorders**: Lymph node pain
- **Cardiac Disorders**: Supraventricular arrhythmias
- **Gastrointestinal Disorders:** Constipation, Gastroesophageal reflux disease, Oral pruritus
- **General Disorders and Administration Conditions:** Edema
- **Hepatobiliary Disorders:** Drug-induced hepatitis
- **Immune System Disorders:** Serum sickness, Hypocomplementemia, Anaphylaxis
- **Infections and Infestations:** Herpes zoster, Paronychia, Pneumonia, Urinary tract infection, Pyuria
- **Investigations**: Blood creatinine increase, Blood potassium increase, Blood urea increase, Heart rate irregular, Urine output decrease, Weight increase
- **Metabolism and Nutrition Disorders**: Hypoalbuminemia
- **Musculoskeletal and Connective Tissue Disorders**: Arthralgia, Groin pain, Muscle spasms

- **Nervous System Disorders**: Ageusia, Dizziness, Sciatica, Cognitive disorder
- **Renal and Urinary Disorders:** Hematuria, Proteinuria, Acute kidney failure, Tubulointerstitial nephritis
- **Respiratory, Thoracic and Mediastinal Disorders**: Cough, Lung infiltration, Pneumonitis, Wheezing
- **Skin and Subcutaneous Tissue Disorders**: Cold sweat, Hyperhidrosis, Rash
- **Vascular Disorders**: Flushing

UBLITUXIMAB + UMBRALISIB COMBINATION

Adverse Events and Potential Risks

The following adverse events were observed in patients treated with the combination of ublituximab + umbralisib and were considered at least possibly related to one or both of the study medications. See the ublituximab and umbralisib investigator brochures for a complete list of all adverse events reported regardless of causality.

Common (>20%)

- **Blood and Lymphatic System Disorders:** Neutropenia
- **Gastrointestinal Disorders:** Nausea, Diarrhea
- **General Disorders and Administration Site Conditions:** Fatigue, Infusion related reaction

Less Common (≥10% - ≤ 20%)

- **Gastrointestinal Disorders:** Vomiting
- **Metabolism and Nutrition Disorders:** Decreased appetite

Uncommon (≥1 - <10%)

- **Blood and Lymphatic System Disorders:** Anemia, Thrombocytopenia, Conjunctival pallor, Hyperbilirubinaemia,
- **Ear and Labyrinth Disorders:** Ear congestion
- **Eye Disorders:** Vision blurred, Corneal edema
- **Gastrointestinal Disorders:** Dyspepsia, Constipation, Abdominal pain, Stomatitis, Abdominal distension, Abdominal discomfort, Salivary hypersecretion, Enterocolitis infectious, Flatulence, Dysphagia, Eructation, Gastrooesophageal reflux disease, Feces discolored
- **General Disorders and Administration Site Conditions:** Oedema peripheral, Asthenia, Pyrexia, Chills, Cold sweat, Face Edema,
- **Hepatobiliary Disorders:** Hypogammaglobulinemia
- **Immune System Disorders:** Urticaria
- **Infections and Infestations:** Pneumonia, Sepsis, Upper respiratory tract infection, Cellulitis, Bronchitis, Conjunctivitis, Oral herpes, Sepsis syndrome, Urinary tract infection, Sinusitis, Clostridium difficile colitis, Otitis media, Rhinovirus infection, Oral candidiasis, Skin infection, Systemic inflammatory response syndrome, Wound
- **Investigations:** Alanine aminotransferase increase, Aspartate aminotransferase increase, Blood creatinine increase, Weight decreased
- **Metabolism and Nutrition Disorders:** Dehydration, Hyperglycemia, Hypokalemia, Hypophosphatasemia, Failure to thrive

- **Musculoskeletal and Connective Tissue Disorders:** Muscle spasms, Muscular weakness Myalgia, Pain in extremity
- **Nervous System Disorders:** Dizziness, Dysgeusia, Headache, Somnolence
- **Psychiatric Disorders:** Anxiety, Nervousness, Agitation, Insomnia
- **Renal and Urinary Disorders:** Micturition urgency, Renal failure, Acute kidney injury
- **Reproductive System and Breast Disorders:** Scrotal cyst, Semen discoloration
- **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea, Cough, Hypoxia, Dysphonia, Lung infiltration, Productive cough, Pneumonitis, Choking, Oropharyngeal pain
- **Skin and Subcutaneous Tissue Disorders:** Alopecia, Rash, Dry skin, Ecchymosis, Pruritus
- **Vascular Disorders:** Hypertension, Epistaxis, Flushing

Events Reported in Less Than 1% of Subjects

- **Infections and Infestations:** Progressive multifocal leukoencephalopathy
- **Metabolism and Nutrition Disorders:** Tumor lysis syndrome
- **Neoplasms Benign, Malignant and Unspecified:** Malignant melanoma
- **Skin and Subcutaneous Tissue Disorders:** Erythrodermic eczematous rash

7.3 CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) dosing and administration guidelines

CHOP chemotherapy and premedications will be administered per institutional guidelines. Patients will receive standard CHOP regimen as follows:

Cyclophosphamide 750mg/m2 intravenously (IV), Doxorubicin 50mg/m2 IV, Vincristine 1.4mg/m2 (maximum total dose of 2mg) IV will be administered on Day 1. Prednisone 100mg daily from Day 1-5 days orally will be administered.

The administration schedule is provided in the table (Table). The amount of drug (in mg) of all the chemotherapy medications will be adminstered based on body surface area (BSA). BSA will be calculated on Day 1 of each cycle. If a patient has >5% change in weight from the previous BSA calculation, then BSA and dose should be recalculated. Full doses of all study medications should be given based on the patient's actual BSA measured on Day 1 of every cycle except for Vincrsitine (dose is capped at 2 mg).

Cyclophosphamide Administration Guidelines:

- Cyclophosphamide will be administered IV over 30 minutes on Day 1
- Refer to approved package insert (PI) for cyclophosphamide storage and preparation
- IV hydration on the day of cyclophosphamide administration is highly recommedned based on institutional guidelines

- Patients who develop hematological toxicities must have their dose adjusted accordingly as follows:

WBC count (μL)	Platelets count(μL)	Dose
>4000	>100000	100% dose
2500-4000	50,000-100,000	50% of dose
<2500	<50,000	Postpone/per instituitional guidelines

Doxorubicine Adminstration Guidelines:

- The recommended life time cummulative doxorubicin dose is 450-550mg/m2
- The maximum dose given on the study will be 300mg/m2
- Before Doxorubicin adminstration, EF of left ventricle MUST be evaluated by Echocardiogram or MUGA scan per institutional standard
- IF EF is <50%, do not adminster doxorubicin
- Doxorubicin is vesicant and should be administered through central line (Mediport or any central venous access)
- Doxorubicin will be adminstered through IV push on Day 1 through central venous access.
- Refer to approved package insert (PI) for Doxorubicin storage and preparation
- Doxorubicin dose must be adjusted based on liver function/bilirubin as follows:

Serum Bilirubin levels	Dose
1.2-3.0 mg/dl	50% dose
>3.0 mg/dl	25% dose

Vincristine Administration Guidelines:

- Vincristine will be administered IV on Day 1 as IV push
- Refer to approved package insert (PI) for vincristine storage and preparation
- In case of severe preipheral neuropathy vincristine should not be administered
- For grade I/II peripheral neuropathy, the dose of vincristine should be decreased per instituitional guidelines or investigator's judgement.

Serum Bilirubin levels	Dose
1.2-3.0 mg/dl	50% dose
>3.0 mg/dl	25% dose

Prednisone Administration and Guidelines:

- Prednisone will be administered orally 100mg daily from Day 1-Day 5 of chemotherapy
- Close monitoring of blood sugars are recommended for those who are diabetics.

7.4 CHOP Chemotherapy Dose adjustments for Elderly (>70 years old):

- Due to the fact that many elderly patients (>70 years old) may not be able to handle full dose of CHOP chemotherapy, dose adjustments on Cyclophosphamide, Doxorubicin and Vincristine may be allowed.
- If the investigator feels that dose of CHOP chemotherapy needs to be reduced, he MUST discuss with sponsor.
- Typically, 25% dose reduction of the standard dose should be considered after discussing with sponsor.

8.0 CONCOMITANT THERAPY:

All therapies other than from study treatments must be reocrded in the concomitant therapy section of CRF.

8.1 Permitted Medications and Supportive Treatment:

- All supportive therapies for medical conditions other than MCL are allowed as clinically indicated.
- Anti-Emetics: Anti-emetics are permitted per institutional standard. Any anti-emetic with potential to prolong, QTc should be use with caution. Frequent monitoring with EKG is highly recommended.
- Anti-Diarrheal: Loperamide is recommended for Grade I diarrhea. For Grade >2 diarrhea, high suspicion for immune colitis should be practiced and treated accordingly.
- Growth Factor: All patients will receive growth factor during the induction chemotherapy. Peg-filgrastim will be administered either on same day or day#2 of chemotherapy per center's standards. Short acting growth factors are also allowed (starting on Day2-10 of every induction treatment).
- Prophylaxis: Viral and Pneumocystis Jirovecii prophylaxis will be given all through the treatment (both induction and maintenance phase)

    - Viral Prophylaxis: All patients will receive Ayclovir (400 BID orally daily) or famciclovir (250mg orally twice a day) or Valacyclovir (500mg orally twice or thrice a day) for prophylaxis.

    - PJP Prophylaxis: Bactrim DS Monday, Wednesday and Friday every week or Dapsone (100mg daily orally)/Atovaquone (1500mg orally daily)/Pentamidine (300mg NEB every 4 weeks) per institution standard. G6PD testing should be done in patients going on Bactrim/Dapsone.

8.2 Excluded Medications:

- Any other systemic anti-neoplastic agent other than U2-CHOP is prohibited on study (e.g. megace, methotraxate, Cox-2 inhibitors and biophosphonates)

8.3 Subsequent Therapies:

- Administration of any other neoplastic therapy apart from U2-CHOP (induction) and U2 (maintenance) is NOT allowed on study unless confirmed progression according to Lugano Lymphoma assessment criteria (Appendix).

- After Progressive disease is established, the patient will be taken off the study and can be treated per investigator's chocie.

9.0 Discontinuation of study, treatment and participation:

9.1 Study Discontinuation:

Patients will be discontinued from study if there is safety concerns indicated by investigator, data safety monitoring board or request to discontinue trial by regulatory or health authroity/IRB or manufacturing difficulties/concerns.

9.2 Treatment Discontinuation:

Phase Ib:

- If patient meets DLT criteria

Phase II:

- Patient experiences treatment related intolerable toxicities that persist despite following the guidelines for dose modifications and dose reductions, including supportive care measures.
    - Treatment may be delayed to recover from toxicity for a maximum of four weeks.
- Confimred Progression of disease based on the response assessment criteria (Appendix)

After withdrawal from protocol treatment, patients should be followed for AEs for 30 calendar days after their last dose of either study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease.

9.3 Study Participation Discontinuation:

- Patient withdraws consent to participate.
- Any reason that in opinion of investigator DSMB or IRB makes subject paarticipation in the study is unsafe or unfeasible.

10.1 Table: 1: Study Assessments and Treatment Schedule (Induction phase)

U2-CHOP-U2 Procedures	Screening (-28 day to -1 day)	Induction Treatment Phase					End of Treatment
		Cycle#1			Cycle#2-6		
		D#1	D#8	D#15	D#1	D#11 (+3 days)	5-6 weeks post C#6
Informed consent	X						
Inclusion/Exclusion Criteria	X						
Demography/Medical History	X						
ECOG Performance status	X	X	X	X	X	X	X
Prior/concomitant Medications	X	X			X	X	X
Comprehensive Physical Exam[1]	X	X		X	X	X	X
Adverse Event assessment			X	X	X	X	X
12 Lead ECG	X				X		
PET/CT	X						X
Bone Marrow Biopsy	X						X[2]
Biopsy-FFPE 15 slides	X						
ClonoSEQ (Adoptive)[3]							X[3]
Laboratory							
Serum Chemistry (CMP, LDH, Uric Acid)[4]	X		X	X	X		X
Hematology (CBC with diff)	X		X	X	X		X
Serology (Hep B, C, HIV, CMV)[5]	X						
Beta 2 microglobulin and Immunoglobulins	X						X
Urine Pregnancy Test	X						
Treatment							
Ublituximab		X	X	X	X		
Umbralisib		X	X	X	X	X	X
PJP Prophylaxis		X	X	X	X	X	X
Viral Prophylaxis		X	X	X	X	X	X
Neulasta		X			X		

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

1: Comprehensive physical exam: Includes height, weight, vitals, full history and physical
2: Bone marrow biopsy at the end of treatment will be performed only if BMBx was positive at the time of diagnosis. Bone marrow aspiration and biopsy MUST include flowcytometry. Histopathological staining must also include cyclin D1. If needed, Fluorescent in situ hybridization (FISH) testing should be done for t(11;14) on biopsy.
3:ClonoSEQ (Adoptive) MRD Assay: For MRD assay, 15 FFPE slides from the diagnostic biopsy and peripheral blood sample from end of treatment (5-6 weeks post C#6) will be sent to Adoptive for MRD assay. For details please refer to MRD section.
4: Serum chemistry includes CMP (Na, K, bicarb, creatinine, Chloride, BUN, Calcium, phosphorus) Liver function tests (AST, ALT, T.Bili, Alkaline Phosphatase), LDH, Uric Acid
5: Hepatitis Serologies include: Hepatitis B (IgM core antibody, IgG core antibody, Surface antigen, Surface antibody), Hepatitis C (Hepatitis C antibody). CMV includes IgG and IgM antibody, HIV: HIV antibody

10.2 Table: 2: Study Assessments and Treatment Schedule (Maintenance phase)
The table below lists all of the required assessments that should be performed at each study visit.

U2-CHOP-U2	U2 Maintenance Phase		End of Treatment
Procedures	**D#1**	**Every 3 month Follow up (3,9,12,15,18,21 and 24 months follow up)**	**30 days post last treatment**
ECOG Performance status	**X**	**X**	**X**
Prior/concomitant Medications	**X**	**X**	**X**
Comprehensive Physical Exam[1]	**X**	**X**	**X**
Adverse Event assessment		**X**	**X**
12 Lead ECG	**X**	**X**	
CT of Neck, Chest, Abd and Pelvis	**X**	**Every 6 months (6,12,18 and 24)**	
Laboratory			
Serum Chemistry [2]	**X**	**X**	**X**
Hematology (CBC with diff)	**X**	**X**	**X**
Beta 2 microglobulin and Immunoglobulins	**X**	**Every 6 months (6,12,18 and 24)**	
Treatment			
Ublituximab	**X**	**X**	
Umbralisib	**X**	**X**	**X**
PJP Prophylaxis	**X**	**X**	**X**
Viral Prophylaxis	**X**	**X**	**X**

1: Comprehensive physical exam: Includes height, weight, vitals, full history and physical
2: Serum chemistry includes CMP (Na, K, bicarb, creatinine, Chloride, BUN, Calcium, phosphorus) Liver function tests (AST, ALT, T.Bili, Alkaline Phosphatase), LDH, Uric Acid

11. STATISTICAL ANALYSIS

This is a Phase Ib/II open label, single arm clinical trial. The primary of objective is to determine the safety and tolerability (Phase Ib), and complete response rate of Umbralisib in combination with Ublituximab-CHOP in Mantle Cell lymphoma (Phase II). The secondar endpoints are to explore PFS, OS at 3 years, disease control rate, rate of MRD negative disease and PFS/OS in MRD negative patients.

11.1 Study design

In the proposed study, the primary endpoint is to estimate the biological response rate of the combination of Umbralisib at dose 800 mg with Ublituximab (900mg)-CHOP, but a phase Ib portion with dose de-escalation at two does level (800 and 600 mg) will be built in to further confirm its safety and tolerability.

Assuming the DLT is no more than ($\leq$) 33% in the combination, the dose de-escalation rule is as following: 3 patients will be evaluated at the first dose cohort, if no DLT occurred, the study will expand to phase II portion; if 1 DLT occurred (in 20 days), additional 3 patients will be evaluated; if <=1 DLT occurred in these three new patients, the study will expand to phase II portion; if >=2 DLT in these three new patients, the dose will be reduced to the lower dose cphort: 3 patients will be evaluated at lower dose (600mg), if no DLT occurred, the study will expand to phase II portion; if 1 DLT occurred (in 3 weeks), additional 3 patients will be evaluated; if <=1 DLT occurred in these three new patients, the study will expand to phase II portion; if >=2 DLT in these three new patients, the study will be terminated.

11.2 Sample size and power justification

Phase Ib safety study will use 3+3 dose de-escalation design at two dose cohorts assuming the DLT is no more than (<=) 33% in the combination. The sample size in this portion will range from 3-12.

We expect that Umbralisib in combination with Ublituximab-CHOP will improve the CRR to 70% comparing to the standard treatment with R-CHOP alone at 40% response rate. Using Single-Stage Phase II design for Testing H0: $P \leq P0$ versus H1: $P \geq P1$, A sample size of 25 achieves 90% power to detect a difference (P1-P0) of 0.3 using a one-sided binomial test. If the number of responses is 15 or more, the hypothesis that P <= 0.4 is rejected with a target error rate of 0.050 and an actual error rate of 0.034. If the number of responses is 14 or less, the hypothesis that P >= 0.7 is rejected with a target error rate of 0.1 and an actual error rate of 0.098.

Thus, a total of 28-35 of patients will be required to both portions of the study.

11.3 Statistical analysis plan

The primary endpoint of response rate will be estimated with binomial distribution along with 2-sided 95% exact confidence intervals with the method of Clopper-Pearson intervals. Frequency and percentage will be presented. KM method will be used to estimate medium PFS, overall survival (OS) and time to response. Analysis of safety data will be descriptive. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Adverse event and serious adverse event (AE/SAE) reporting during the study

will be summarized by relationship to study drug and intensity by dose cohorts. Number and proportion of adverse event, serious adverse event and grade 3 or 4 lab toxicity will be reported by body system. Patient's baseline lab data and its change during treatment at each visit will be presented. Graphic statistics tool such as
box plot will be used when it is appropriate.

12. DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION:

- Tumor and efficacy assessment will be based on Positron Emission Tomography (PET)/Computed Tomography (CT) Scans criteria based on cheson 2014 (appendix) at indicated times (table).
- Positron Emission Tomography (PET)/Computed Tomography (CT) Scans will be peformed at screening (within 28 days of beginning of treatment) and 5-6 weeks post C#6.
- The criteria for response assessment are listed in appendix.
- Bone marrow apsiration and biopsy will be peformed at the screening. If positive, it will be repeated at end of treatmnet (EOT, 5-6 weeks post C#6)
- Minimal residual disease assessment will be done 5-6 weeks post C#6 (End of treatment-EOT). Both FFPE sample from diagnostic biopsy (lymphnode/extranodal tissue, 15 slides) with peripheral blood sample MUST be provided. The shipping box and label will be provided by Adoptive Biotechnologies (South San Francisco, CA) directly to the site upon request.
- During the maintenance period, patients will be followed by CT/MRI of Neck, chest, abdomen and pelvis with contrast every 6 months. If renals function is not permitting, without contrast scans (CR/MRI) are allowed.

13. MINIMAL RESIDUAL DISEASE ASSESSMENT:

The ClonoSEQ® assay by Adaptive Biotechologies (South San Francisco, CA), developed by Sequenta and previously called ClonoSIGHT®, will be used to identify clonal immunoglobulin DNA sequences unique to a patient's lymphoma, which will then be used to determine the existence of minimal residual disease (MRD) in the peripheral blood of patients following induction. ClonoSEQ® is a novel, deep sequencing-based method to identify cells with specific molecular signatures. This will be used to determine the patients' response to therapy and to determine eligibility for this clinical trial. The patient-specific rearrangement can be determined from a sample with high disease load, e.g., the diagnostic sample. The level of the specific clone can then be determined with high sensitivity and specificity in different samples in the patient. Detection of minimal residual disease can help inform the patient's response as well as detection of relapse. The details of the assay can be found at https://www.adaptivebiotech.com/clonoseq/clonoseq-assay

MRD status is an exploratory endpoint for this trial. Peripheral blood samples are required at the end of induction treatment (within 4-6 weeks post induction treatment).

14.0 SAFETY REPORTING

Reporting Serious Adverse Events to TG Therapeutics and FDA

The definitions of serious adverse events (SAEs) are given below. The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.
An SAE or reaction is defined as any untoward medical occurrence that results in any of the following:

- Death,
- Life-threatening adverse event,
- Inpatient hospitalization of at least 24 hours, or prolongation of existing hospitalization,
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

SAE Reporting to TG Therapeutics

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

SAE Reporting to the FDA and IRB

Investigator is responsible for reporting relevant SAEs to the FDA. Investigator is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the FDA within 7 calendar days after being notified of the event. Investigator will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs (SUSAR) associated with the use of the study medications to the FDA by a written safety report within 15 calendar days of notification. Investigators must report SUSARs and follow-up information to their responsible Institutional Review Board (IRBs)/Independent Ethics Committee according to the policies of the responsible IRB (Research Ethics Committee).

The following are events of special interest, and will need to be reported expeditiously:
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 an SAE form to TG Therapeutics at safety@tgtxinc.com within 24 hours of the first knowledge of the event by the treating physician or research personnel. Abortions (spontaneous, accidental, or therapeutic) must also be reported to TG Therapeutics at safety@tgtxinc.com within 24 hours of awareness.

Study Drug Overdose

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

Secondary / Second Malignancy

Any secondary or second malignancy event must be reported to TG Therapeutics at safety@tgtxinc.com via the SAE form within 24 hours of awareness.

15. REGULATORY, ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 Prestudy Document Requirements:

Participating study sites cannot begin enrollment until an initiation letter has been issued from the UAB CTNMO. Each center is required to participate in an initiation conference call. Before the start of this study and the shipment of study drug to a participating study site, the following documents must be on file at UAB CTNMO. Participating sites will be responsible for forwarding the initiation documents toUAB CTNMO. All start-up documents can be submitted via electronic mail to pamdixon@uab.edu or via fax at (205) 975-9875. Please ensure that the fax cover page clearly identifies the site, study identifier and is addressed to ATTN: UAB CTNMO.

These documents are required to be submitted by each participating center:

1. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator at the participating center.

2. The names of any sub-investigators at the participating center must appear on e 1572. Investigators must also complete all regulatory documentation as required by local regulations. This includes any required human subjects training required by the site's local IRB.

3. Current curricula vitae and documentation of professional licensure of the Principal Investigator and sub-investigators listed on the 1572.

4. Resumes and human subject protections documentation (e.g. NIH, CITI) for all research personnel (e.g. study coordinators, data managers and other research personnel) and documentation of ICH-GCP training.

5. A signed and dated investigator brochure acceptance form.

6. Written documentation of IRB approval of protocol (identified by title, protocol version and date of approval) for each site.

7. IRB approved study informed consent and HIPAA consent form. HIPAA consent language can be included within the study informed consent. Please note that all informed consent forms should be reviewed and approved by the UAB CTNMO prior to submission to the site's designated IRB.

8. A signed Confidentiality Agreement.

9. A signed Clinical Trial Agreement for each site.

10. Laboratory certifications (CAP, CLIAs) and laboratory reference value ranges for each laboratory listed on the site's 1572.

11. The UAB CTNMO site specific forms as specified in the investigator-initiated multicenter manual.

15.2 Compliance with Law and Regulation

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements. This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide TG Therapeutics with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to TG Therapeutics, with copy to UAB CTNMO

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The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected. TG Therapeutics will provide study sites with any expedited safety reports generated from any ongoing studies with carfilzomib, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of carfilzomib during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study. Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee, TG Therapeutics with a summary of the trial's outcome.

15.3 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.

15.4 Ethical, Financial, and Regulatory Considerations

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

15.5 IRB Approval

The study protocol, the informed consent form and other necessary study documents must be submitted to the IRB for ethical review and approval prior to the study start. Principal Investigator is also responsible for insuring IRB renewals, and IRB approval for all subsequent protocol amendments and changes to the informed consent document. Copies of the initial IRB approval letter and IRB approved ICF must be provided to TG Therapeutics prior to the study start. Copies of any subsequent IRB approval letters and IRB approved ICFs must also be provided to TG Therapeutics as they become available.

15.6 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A copy of the

informed consent form, to include the patient's signature, will be provided by the investigator to the patient. 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 must be obtained.

15.7 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws. HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization from the study that he or she has been informed of following:

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

15.8 Data Recording:

The Clinical Research Coordinator and Investigator will be responsible for the recording of all data on the electronic Case Report Forms (eCRFs) on OnCore system. The Investigator will provide access to his/her original records to permit a representative from the funding or auditing institution(s) to verify the proper transcription of data. Data submission will be electronically via Fax or email.

15.9 Study Monitoring:

CTNMO will be responsible for the monitoring of study patient data and records. Monitoring will be performed centrally. All monitoring reports will be kept by the UAB CTNMO to ensure that all reports are contained in a central study file. The CTNMO manager or UAB internal auditor will be responsible for conducting the review of monitoring packets. A final monitoring report will be generated and issued to the site and will be kept in the central study file by the UAB CTNMO.

15.10 Frequency of Reviews:

The each patient at each participating center will have their eligibility criteria reviewed prior to enrollment by the UAB CTNMO. During the course of the study, each site will be selected for an audit by the UAB Quality Assurance Committee approximately once a year. Audit will include 10% of the subjects enrolled at the site. In addition to the once yearly QA audit, monitoring for each patient entered into this trial will be 100%. Sites are to send source information on each patient to the UAB CTNMO office where a shadow chart will be maintained on each subject for this trial. Source will be verified to data entered into the OnCore database.

15.11 Protocol Deviation and Safety reporting:
The University of Alabama Comprehensive Cancer Center Data Safety Monitoring Board will have oversight of the protocol. The UAB CCC DSMB will meet at a minimum on a monthly basis to discuss hematology related trials. In addition, all protocol deviations and SAEs as defined above will be reviewed by the UAB CCC DSMB for review during the DSMB monthly meetings. The coordinating center will review protocol deviation and SAE events for form completion and provide assistance in communicating to the subsite if more information is warranted. The UAB CTNMO will report the event report to the UAB CCC DSMB so that the information can be reviewed at the next available DSMB meeting. During the DSMB review, the DSMB can make recommendations for any further study action.

15.12 Data Collection:
Data collection will be managed by the UAB CTNMO staff via the study database which is housed and maintained at UAB Cancer Center. Time sensitive information such as patient registration, serious adverse events reporting, and protocol deviation reporting will be collected via completed hard copy form. These forms are available from the UAB CTNMO. . Information collected will be reviewed and processed by the UAB CTNMO.

The data will be initially reviewed for quality assurance purposes to identify any discrepancies or missing data. The staff of the UAB CTNMO will notify the participating site of any data queries and manage the overall data quality of the study. If data received relates to a serious adverse event or protocol deviation, the information will be processed for report to the UAB CCC DSMB for review. The sponsor- investigator, Luciano Costa, MD and the assigned statistician, will also have access to study data for quality assurance and analysis purposes. During the course of the study, data quality will be monitored by random inspection of the completed forms by a designated monitor. Any problems detected will be discussed with the PI. If necessary, re-training of data collectors will be conducted.

All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed. The study will be subject to a yearly internal audit via the UAB CCC Quality Assurance Committee at a minimum and audits may occur more frequently at the request of the QA Committee.

15.13 Study Completion:

The following data and materials are required by UAB CTNMO , TG Therapeutics before a study can be considered complete or terminated:

1. Copies of protocol amendments and IRB approval/notification, if appropriate.
2. Copies of the IRB final report, documentation of submission to the IRB.
3. A summary of the study prepared by the Principal Investigator (Study report, manuscript and/or abstract).
4. All regulatory documents (e.g., updated curriculum vitae for each Principal Investigator, updated U.S. FDA Form 1572 for each site).

15.14 Record Retention:
Federal law requires that an Investigator maintain all study records for two years after the investigation is discontinued.

15.15 Publication

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

References:

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-18.
2. Zhou Y, Wang H, Fang W, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer 2008;113:791-8.
3. Caballero D, Campo E, Lopez-Guillermo A, et al. Clinical practice guidelines for diagnosis, treatment, and follow-up of patients with mantle cell lymphoma. Recommendations from the GEL/TAMO Spanish Cooperative Group. Ann Hematol 2013;92:1151-79.
4. Jares P, Colomer D, Campo E. Molecular pathogenesis of mantle cell lymphoma. J Clin Invest 2012;122:3416-23.
5. van de Schans SA, Janssen-Heijnen ML, Nijziel MR, Steyerberg EW, van Spronsen DJ. Validation, revision and extension of the Mantle Cell Lymphoma International Prognostic Index in a population-based setting. Haematologica 2010;95:1503-9.
6. Bosch F, Lopez-Guillermo A, Campo E, et al. Mantle cell lymphoma: presenting features, response to therapy, and prognostic factors. Cancer 1998;82:567-75.
7. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008;111:558-65.
8. Stefancikova L, Moulis M, Fabian P, et al. Loss of the p53 tumor suppressor activity is associated with negative prognosis of mantle cell lymphoma. Int J Oncol 2010;36:699-706.
9. Kienle D, Katzenberger T, Ott G, et al. Quantitative gene expression deregulation in mantle-cell lymphoma: correlation with clinical and biologic factors. J Clin Oncol 2007;25:2770-7.
10. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica 2009;94:1555-62.
11. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol 2005;131:29-38.
12. Angelopoulou MK, Siakantariz MP, Vassilakopoulos TP, et al. The splenic form of mantle cell lymphoma. Eur J Haematol 2002;68:12-21.
13. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009;27:1209-13.
14. Dreyling M, Thieblemont C, Gallamini A, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol 2013;24:857-77.
15. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood 2009;113:4144-52.
16. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005;23:1984-92.
17. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687-93.
18. Lefrere F, Delmer A, Levy V, Delarue R, Varet B, Hermine O. Sequential chemotherapy regimens followed by high-dose therapy with stem cell transplantation in mantle cell lymphoma: an update of a prospective study. Haematologica 2004;89:1275-6.
19. Harel S, Delarue R, Ribrag V, Dreyling M, Hermine O. Treatment of younger patients with mantle cell lymphoma. Semin Hematol 2011;48:194-207.
20. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood 2013;121:48-53.
21. Hermine O, Hoster E, Walewski J, et al. Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net). 2012.

22. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol 2010;150:200-8.
23. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. Ann Oncol 2013;24:1587-93.
24. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med 2012;367:520-31.
25. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-10.
26. Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. J Clin Oncol 2013;31:1442-9.
27. Michael Wang LIG, Simon Rule, Andre Goy, Olivier Hermine, Aleksandra Rizo, Sen Hong Zhuang, Martin H. Dreyling. A phase III study of ibrutinib in combination with bendamustine and rituximab (BR) in elderly patients with newly diagnosed mantle cell lymphoma (MCL). Journal of Clinical Oncology 2013.
28. Franco Cavalli BR, Lixia Pei, Helgi Van De Velde, Tadeusz Robak,. Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT). Journal of clinical oncology 2014;32:8500.
29. Jantunen E, Canals C, Attal M, et al. Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol 2012;23:166-71.
30. Lefrere F, Delmer A, Suzan F, et al. Sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation induces a high rate of complete response and improves event-free survival in mantle cell lymphoma: a prospective study. Leukemia 2002;16:587-93.
31. Khouri IF, Saliba RM, Okoroji GJ, Acholonu SA, Champlin RE. Long-term follow-up of autologous stem cell transplantation in patients with diffuse mantle cell lymphoma in first disease remission: the prognostic value of beta2-microglobulin and the tumor score. Cancer 2003;98:2630-5.
32. Pott C, Hoster E, Delfau-Larue MH, et al. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. Blood 2010;115:3215-23.
33. Kahl BS, Longo WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. Ann Oncol 2006;17:1418-23.
34. Chang JE, Peterson C, Choi S, et al. VcR-CVAD induction chemotherapy followed by maintenance rituximab in mantle cell lymphoma: a Wisconsin Oncology Network study. Br J Haematol 2011;155:190-7.
35. Hoellenriegel J, Meadows SA, Sivina M, et al. The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia. Blood 2011;118:3603-12.
36. Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood 2011;117:591-4.
37. Meadows SA, Vega F, Kashishian A, et al. PI3Kdelta inhibitor, GS-1101 (CAL-101), attenuates pathway signaling, induces apoptosis, and overcomes signals from the microenvironment in cellular models of Hodgkin lymphoma. Blood 2012;119:1897-900.
38. Liu N, Rowley BR, Bull CO, et al. BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110alpha and p110delta activities in tumor cell lines and xenograft models. Mol Cancer Ther 2013;12:2319-30.
39. Kahl BS, Spurgeon SE, Furman RR, et al. A phase 1 study of the PI3Kdelta inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). Blood 2014;123:3398-405.
40. Preliminary results of a phase II study of single agent Bay 80-6946, a Novel PI3K inhibitor, in patients with relapsed/refractory, indolent or aggressive lymphoma. Clin Adv Hematol Oncol 2014;12:14-6.

Additional References:

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

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

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

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

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

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

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

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

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

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

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

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

Prasanna R, V. S. (2011). *PI3Kgamma enzyme assay.* Shameerpet, India: Incozen Therapeutics.

Seeta N, V. S. (2011). *AKT phosphorylation in MOLT-4 cells. June Study Report IVT-5264-APM-10.* Shameerpet, India: Incozen Therapeuticis PVT Ltd.

Seeta N, V. S. (2011). *AKT phosphorylation in THP-1 cells. Study Report IVT-5264-ATP-08.* Shameerpet, India: Incozen Therapeuticis PVT Ltd.

Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, Au WY, et al. Follicular Lymphoma International Prognostic Index. Blood. 2004; (104)5: 1258-65.Therapeutics, T. (2017). Ublituximab (TG-1101) and TGR-1202 Investigator's Brochure (Vol. Version 5.0).

APPENDIX

APPENDIX: A

CONTRACEPTION GUIDELINES AND PREGNANCY

Females Not of Childbearing Potential are Defined as Follows:

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

Contraceptive Guidelines for Females of Child-Bearing Potential:

Females of child-bearing potential, defined as all females physiologically capable of becoming pregnant, must use effective contraception during the study and for 4 months after the last dose of either study treatment. Effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the 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 ≤ 72 hours

prior to initiating treatment.

Fertile Males

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

Pregnancies

To ensure 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 should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

APPENDIX B: NEW YORK HEART ASSOCIATION CLASSIFICATION

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

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

APPENDIX: C Hepatitis B Serologic Test Results

Interpretation of Hepatitis B Serologic Test Results

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

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

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

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

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

CDC

www.cdc.gov/hepatitis

APPENDIX D: Mantle Cell Lymphoma IPI (MIPI)

Points	Age, y	ECOG	LDH, ULN	WBC, 10^9/L
0	< 50	0-1	< 0.67	< 6.700
1	50-59	–	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000-1.49	1.000-14.999
3	≥ 70	–	≥ 1.5000	≥ 15.000

- For each prognostic factor, 0-3 ponts are given. The ponts are summed up to total of max 11.
- Total score: 0-3 is considered low risk, 4-5 is considered intermediate risk and patients with 6-11 points are considered ar high risk

EASTERN COOPERATIVE GROUP PERFORMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

APPENDIX E: CHESON ET AL, RESPONSE ASSESSMENT FOR LYMPHOMA (2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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	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	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	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
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 1 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 (eg, 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

(continued on following page)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, 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; 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 score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). 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 (eg, 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†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.

ANN ARBOR STAGING FOR LYMPHOMA

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

APPENDIX E: CTAE.

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

Date: 6/28/23

Subject: Final Report on NCT04692155 (Phase I/II trial of Ublituximab with CHOP followed by U2 maintenance in previously untreated MCL.

IRB#300006404

This was an investigator initiated trial in Untreated Mantle Cell lymphoma patients who are ineligible for consolidative Autologus stem cell Transplant. This trial was terminated in September 2022 due to toxicity concerns. The umbralisib was associated with high risk of COVID related mortality as shown in other trials. Therefore, this trial was initially on hold by FDA but then was terminated.

We enrolled only 1 patient who had advanced Mantle Cell Lymhoma. He completed 3 cycles of U2-CHOP but then developed grade 5 event with COVID PNA and passed away.

Ref: https://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-voluntary-withdrawal-blasnda-u2-treat