Protocol Title: A Single-center Phase IIa Study Evaluating the Safety and Tolerability of Umbralisib and Ibrutinib in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma

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DRUG REIMBURSEMENT / ACQUISITION:
Ibrutinib 560 mg orally daily up to a year x 24 subjects supplied to investigators by Janssen Scientific Affairs, LLC (Janssen)
Umbralisib orally daily up to a year x 24 subjects is an investigational agent supplied to investigators by TG Therapeutics
Correlative Studies: Covered by Janssen Scientific LLC and TG Therapeutics external funding. (*Pretreatment core guided biopsy of accessible lymph node: Core and FNA Fresh & FFPE; Day 8 & at time of Progression of Disease (PD): US guided biopsy of accessible lymph node, FNA Fresh & FFPE Pathology processing and Flow cytometry)*
Per Subject and Administrative Costs: Cost share between Janssen Scientific LLC and TG Therapeutics

Protocol Format

NIH designated Clinical Cancer Centers must conduct scientific peer review of clinical protocols. A standardized protocol format is used for the successful implementation of this process. All Fred & Pamela Buffett Cancer Center Investigator-initiated Institutional and Multi-Institutional protocols developed and sponsored by this institution involving clinical research must include the following elements or the equivalent:

Appendices:

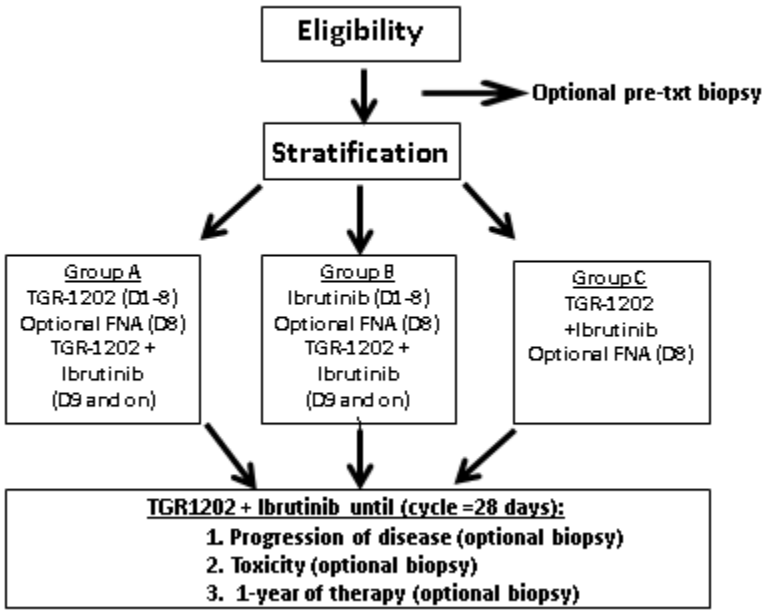
Abstract:

Title: A Single-center Phase IIa Study Evaluating the Safety and Tolerability of Umbralisib and Ibrutinib in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma: A Trial of the Lymphoma Precision Medicine Laboratory

Lymphomagenesis is known to be a result of aberrant signaling through the B-cell receptor (BCR). Several models have highlighted specific checkpoints that appear to be regulators of downstream signal propagation leading to abnormal nuclear transcription within the lymphocyte leading to either anti-apoptosis or a proliferative advantage. A better understanding of the BCR signaling pathway in malignant lymphocytes has led to several small molecule inhibitors entering clinical practice as single agents for the treatment of non-Hodgkin lymphoma (NHL). Two classes of BCR antagonists have shown strong activity in (NHL): Bruton's Tyrosine Kinase (BTK) and phosphoinositide-3-kinase (PI3-K) delta inhibitors. Ibrutinib is a first generation selective and irreversible inhibitor of BTK. umbralisib (formerly known as TGR-1202) is a PI3-K delta inhibitor with a novel structure unlike other PI3K inhibitors affording once daily dosing and to date a unique toxicity profile. Attacking the aberrant BCR signaling pathway at separate nodes may be an important mechanism to overcome chemorefractory NHL. This is a single-center Phase IIa study evaluating the safety and tolerability of umbralisib and Ibrutinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). We plan to accrue 24 patients. The primary endpoint in this phase IIa study is to consecutively monitor the safety and tolerability of the oral doublet and allow a preliminary assessment of the efficacy of this novel combination to provide background for an appropriately powered phase II or phase III study. There will be 3 treatment groups given one year (12 months) of therapy, Group A (consented to optional biopsies; 6 patients): umbralisib800 mg PO daily on Days 1-8; then umbralisib 800 mg oral daily and Ibrutinib 560 mg oral daily; Group B (consented to optional biopsies; 6 patients): Ibrutinib 560 mg PO daily Days 1-8; then umbralisib 800 mg PO daily and Ibrutinib 560 mg PO daily; and Group C (deferred consent to optional biopsies or consented to optional biopsies; 12 patients): umbralisib 800 mg PO daily and Ibrutinib 560 mg PO daily. Secondary endpoints of the trial will be assessment of the overall response rate (ORR) defined as the sum of complete responses (CR) and partial responses (PR) and to determine the progression-free survival (PFS), time to response (TTR), and duration of response (DOR) in patients with relapsed or refractory DLBCL.

Schema:

Title: A Single-center Phase IIa Study Evaluating the Safety and Tolerability of Umbralisiband Ibrutinib in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma



Group A (consented to optional biopsies; 6 patients): umbralisib 800 mg PO daily on Days 1-8; then umbralisib 800 mg oral daily and Ibrutinib 560 mg oral daily

Group B (consented to optional biopsies; 6 patients): Ibrutinib 560 mg PO daily Days 1-8; then umbralisib 800 mg PO daily and Ibrutinib 560 mg PO daily

Group C (deferred consent to optional biopsies or consented to optional biopsies; 12 patients): umbralisib 800 mg PO daily and Ibrutinib 560 mg PO daily

Duration of therapy

In the absence of treatment delays due to adverse event(s), treatment should continue unless one of the following criteria applies:

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

A cycle is 28 days of treatment with any oral agent regardless of group assignment. The first efficacy assessment should be approximately 8 weeks after Cycle 1/Day 1 (+/- 7 days). Thereafter efficacy assessment will occur approximately every two months until 6 months then every 3 months until completion of 12 months of treatment (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion.

Section 1.0 Objectives:

Primary objective:

1. To determine the safety and tolerability of umbralisib and ibrutinib in relapsed and refractory (rel/ref) DLBCL

Secondary objectives:

1. To determine the overall response rate (ORR) defined as the sum of complete responses (CR) and partial responses (PR).
2. To determine the event-free survival (EFS), time to response (TTR), and duration of response (DOR) in patients with rel/ref DLBCL.

Exploratory objectives:

1. To evaluate molecular profiling of patient samples (optional lymph node biopsies) obtained at days 0 (pre-treatment; core biopsy), day 8 (fine needle aspiration) and end of treatment (progressive disease or end of study treatment—1 year; core biopsy) to evaluate the baseline characteristics and dynamic shifts in mutational landscape, transcriptional signatures and intracellular signaling cascades in primary tumor cells.
   (i) Next generation sequencing to define the mutational status of 384 genes that mutated in DLBCL, including CD79B, CARD11, and MYD88;
   (ii) Transcriptional profiling to evaluate signatures of B-cell receptor signaling and the back-up pathway of oxidative phosphorylation.
   (iii) Phospho-specific flow cytometry to measure the basal and induced level of activation of components within parallel signaling pathways downstream of the B-cell receptor.
   (iiii) Monitor changes in T- cell characteristics in response to exposure to umbralisib and ibrutinib
2. To perform quantitative response evaluation by peripheral blood cell-free DNA sequencing at enrollment, day 8, 1 month, at every response assessment time point compared to standard radiographic response evaluation by PET/CT or CT and end of treatment (progressive disease or end of study treatment—1 year). After month 12, efficacy assessments should occur at the investigators discretion with collection of a research blood sample only if feasible.
3. To evaluate the genetic profiling for drug resistance mutations
4. To evaluate DLBCL subtype analysis by immunohistochemistry compared to Nanostring assessment

Section 2.0 Introduction:

2.1 Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLCBL) remains the most common non-Hodgkin lymphoma (NHL) diagnosed per annum with an increasing prevalence, now noted to be approximately 500,000 individuals (http://seer.cancer.gov/stat/facts/html/leuks.html). Nearly 40% of those individuals are older than 70 years of age. Patients with DLBCL presents most commonly with advanced stage disease and without treatment are nearly uniformly lethal. However current multiagent immunochemotherapy regimens do provide a curative option for those able to receive treatment. The most common combination chemo-immunotherapy is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), which now cures nearly two-thirds of patients.(1) The prognosis is dependent on many patient specific factors most accurately defined by the International Prognostic Index (IPI) and by recent disease specific characteristics defined as molecular subtyping into either Germinal Center B-cells (GCB) or Activated B-cell like (ABC).(2, 3) In the current treatment era the overwhelming majority of patients will be exposed to a rituximab containing induction regimen. Despite aggressive up front treatment nearly one-third of patients with DLBCL will have refractory disease or experience a relapse of DLBCL. A second chance at cure is maintained with second line therapy in addition to high dose therapy and autologous stem cell rescue (HDT-ASCR) in those who are transplant eligible. However, only 1 in 4 patients who undergo transplant will achieve long-term disease control and subsequent chemotherapy regimens yield diminishing returns and often serve as a bridge towards allogeneic transplantation if eligible and/or available.(4) Patients who are not considered transplant eligible suffer a dismal prognosis with no

standard of care to help guide treatment choices. Therefore, a substantial number of highly chemotherapy refractory patients remain in search of further therapy that can preserve the balance of quality and quantity of life.

2.2 B-cell receptor Pathway

The B-cell receptor pathway is a complex network of enzymatic checks and balances that regulate B-cell maturation and subsequent migration.(5) Many points of divergence exist within the network creating parallel streams of potential reflexive regulation. Tonic stimulation of an enzymatic node by mutations within the protein can be a lymphoma generating event. This has been further expounded by the molecular profiling of DLBCL. The results have led to the defining of 3 different molecular subtypes of DLBCL in which the BCR pathway plays a significant role: 1) Germinal Center B-cell (GCB), 2) Activated B-cell like (ABC), and 3) Unclassifiable.(3) The GCB subtype is felt to be more attracted to the phosphoinositol-3 kinase pathway.(6) The ABC subtype of DLBCL appears to be addicted towards the downstream pathway leading towards the Nfk-B stimulation and subsequent nuclear transcription.(7) The GCB subtype of DLBCL represents nearly two-thirds of all DLBCL cases and has a more favorable prognosis than ABC DLBCL. These downstream pathways have become clinically relevant targets with several drugs attempting to inhibit these processes.

2.3 Targeting the B-cell receptor pathway

Success with small molecule inhibitors that abrogate the abnormal signaling through the BCR pathway has brought upon an exciting paradigm shift in the management of B-cell NHL. Several novel non-chemotherapeutic drugs now attack the malignant lymphocytes via mechanisms unperturbed or selected for by prior non-selective chemotherapy or exposure to CD20 directed monoclonal antibodies (Figure 1). Currently these drugs are in the clinic as single agents or combined with a CD20 monoclonal antibody. This includes but not limited to the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib and the PI3-K inhibitor, Idelalisib. Both BTK and PI3-K have several next generation antagonists in clinical development. Umbralisib is a next generation PI3-K delta inhibitor with a novel structure different than other PI3-K inhibitors in development. This structure may lead to differential activity and toxicity profile than previously seen in other PI3-K inhibitors. Current data supports that BTK inhibitors may provide selective activity towards the ABC subtype of DLBCL whereas PI3-K inhibitors may provide selective activity to the GCB subtype of DLBCL.(8)

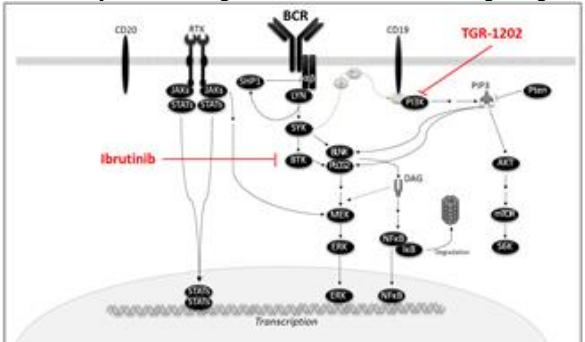


Figure 1. Parallel pathways downstream of the B-cell receptor (BCR). BCR signaling induced a phosphorylation cascade that feeds through the proximal BCR signaling components LYN, SYK, BTK, BLNK and PLCG2. This activates the MEK-ERK MAP kinase cascade, as well as parallel survival pathways such as the NFκB and PI3K pathways. Activity of the NFκB pathway is regulated by IκB, which is phosphorylated and degraded upon pathway activation and allows phosphorylation and nuclear accumulation of NFκB transcription factors such as p65. The PI3K pathway is regulated by PTEN, and activates phosphorylation of Akt, mTOR, and S6 kinase. The targets of Ibrutinib (BTK) and TGR-1202 (PI3Kδ) are shown. It can also be seen that signaling into the PI3K pathway can occur upstream of the Ibrutinib target, BTK, allowing activation of this important survival pathway in the presence of BTK inhibition (green arrows). This provides a rationale for dual inhibition of these parallel pathways.

Currently targeted agents against the BCR have been primarily explored as single agents or in combination with a CD20 monoclonal antibody. Results have shown that as a single agent each may be potent enough to achieve disease control in indolent NHL, like follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).(9) However, treatment of relapsed/refractory (rel/ref) DLBCL especially after HDT-ASCR or in transplant ineligible patients remains a difficult situation with a poor overall prognosis. Combinations of novel agents that do not have cumulative toxicities are likely needed to overcome the clonal complexity and aggressive biology that prevents durability in the rel/ref DLBCL. The novel chemo-free oral combination of umbralisib and Ibrutinib may be an attractive combination for the treatment of this difficult to treat population.

2.4 Rationale for a phase IIa design

Both BTK and PI3-K inhibitors that are in current practice have been developed under a continuous dosing scheme in an attempt to chronically antagonize the BCR pathway. As drugs progress through phases of clinical trials it is well established dogma that a maximum tolerated dose (MTD) is the objective in phase I studies. However, this only reports

dose limiting toxicities (DLT) during the initial cycle of therapy when further cumulative toxicities may be seen in subsequent cycles that limits the utility of a regimen. Therefore, in paradigms were long-term safety and tolerability is paramount and needed to balance with objective responses phase IIa studies can be employed to not only provide this tolerability signal but inform future studies that lead to appropriately powered and better informed phase II or phase III studies. Therefore, we must balance efficacy while limiting cumulative toxicities events (CTE).

2.1 Umbralisib

Umbralisib (formerly known as TGR-1202) is a highly specific and orally available PI3K delta inhibitor with high selectivity over the alpha, beta, and gamma isoforms of PI3K. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in NHL. Umbralisib has demonstrated safety in an ongoing Phase I clinical trial in patients with NHL and chronic lymphocytic leukemia (CLL).(10) umbralisib is manufactured by Alembic Pharmaceuticals and is being supplied by TG Therapeutics, Inc.

2.1.1 [redacted]

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2.1.4 Clinical development of TGR 1202 in hematologic malignancies

2.1.4.1 Umbralisib monotherapy

Umbralisib is being evaluated in multiple studies. The first in human phase I dose-escalation study with expansion cohorts in rel/ref hematologic malignancies patients has accrued approximately 55 patients. Umbralisib at doses ranging from 50 mg to the micronized 1800 mg QD dose has been tested. umbralisib is available as 200 mg tablets, as this study progressed to higher dose levels this resulted in an unfavorable number of tablets for daily administration. In an effort to improve the oral bioavailability of umbralisib and pill count, the particle size of the drug product was reduced through a micronization process. The micronization process resulted in greater absorption (approximately 3 fold in a 24 patient healthy volunteer bioequivalence study).

In this study adverse events (AEs) have been manageable, with Grade 3/4 AEs occurring in >10% of patients consisting of the following (March 2015) regardless of attribution to umbralisib: neutropenia, rash, dyspnea, thrombocytopenia, and diarrhea. Of note, a Grade 3 AE of rash was reported in a patient in the non-micronized 800 mg dose cohort who was on concomitant antibiotics. This patient had a history of antibiotic related rash. All medications were held until the rash resolved and they were re-challenged at the 800 mg dose of umbralisib with no recurrence of rash. However, this event met the criteria for a DLT as stated in the protocol and subsequently 3 additional patients were treated at the 800 mg dose, with no additional DLT's reported.

On this study the safety data has now been obtained on patients dosed with umbralisib daily for over a year with no safety concerns recognized or reported as documented by the Study Chair and Medical Monitor for the trial up through the micronized 1200 mg QD dose. Dosing continues in this study using the micronized formulation of umbralisib.

2.1.4.2 Umbralisib + anti-CD20 monoclonal antibody, ublituximab

Umbralisib continues to be evaluated in the phase 1/1b dose escalation study with the glycoengineered anti-CD20 monoclonal antibody ublituximab (UTX).(10) Fifty-seven patients have been enrolled and are evaluable for safety. AEs (AE; all causality) include: Day 1 infusion related reactions, neutropenia, diarrhea, nausea. To date, umbralisib related hepatotoxicity has not been reported in this study. No DLTs have occurred in the NHL cohort. A possible dose-response relationship has been observed between "lower" and "higher" umbralisib doses. A higher dose was defined as greater than 800 mg of the non-micronized umbralisib. To date, 89% of pts (16/18) in the "high" dose cohorts remain on study progression free compared to 57% (8/14) in the "low" dose cohorts. This study continues to enroll in expansion cohorts in NHL subtypes with umbralisib at a micronized dose of 800 and 1200 mg plus UTX.

2.2 Ibrutinib

Ibrutinib is indicated for the treatment of: 1) patients with chronic lymphocytic leukemia (CLL) 2) patients with chronic lymphocytic leukemia (CLL) with 17p deletion; 3) patients with mantle cell lymphoma (MCL) who have received at least one prior therapy (accelerated approval was granted for this indication based on overall response rate, continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials; 4) patients with Waldenström's macroglobulinemia (WM). 5) Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. Ibrutinib is not approved in the disease state being studied here.

2.2.1 Chemical structure and description of Ibrutinib

Ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib is a white to off-white crystalline solid. It has a single chiral center and is the R-enantiomer. The investigational drug product, ibrutinib, is an oral formulation containing micronized ibrutinib. Ibrutinib is manufactured by Pharmacyclics, Inc. and is being supplied by Janssen Scientific Affairs, LLC.

2.2.2 In vitro data of ibrutinib

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity.(12) In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of both BTK and phosphorylation of BTK's physiological substrate, phospholipase-C gamma (PLCγ).22 In DLBCL cell lines ibrutinib inhibited the proliferation at a median effective concentration of 1 to 2 nM.(13)

2.2.3 Pharmacology/Toxicology

Ibrutinib's bioavailability is relatively low and quite variable. A mass-balance study (PCI-32765CLL1004) demonstrated that ibrutinib 140 mg (admixed with 14C-ibrutinib) showed approximately 90% of radioactive ibrutinib was excreted within 168 hours after administration, with less than 10% accounted for in urine and the remainder in feces. A negligible fraction was excreted as unchanged drug.

Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child

-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of ibrutinib has not been evaluated in patients with hepatic impairment. Monitor patients for signs of ibrutinib toxicity and follow dose modification guidance as needed. It is not recommended to administer ibrutinib to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C).

Ibrutinib is metabolized primarily by CYP3A. Drug-drug interaction study has demonstrated that when ibrutinib was administered at a 120 mg dose in combination with 40 mg of ketoconazole, a strong CYP3A inhibitor, the last concentration quantifiable (AUCO-last) was extended up to 29 times longer than without ketoconazole exposure. Terminal half-life was not increased. Therefore, use of strong CYP3A inhibitors is not allowed and guidance on concomitant use of ibrutinib with other CYP3A inhibitors or inducers is provided in the Appendix A.

Absorption
Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) observed in patients at 560 mg is 953 ± 705 ng·h/mL and in patients at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib Cmax and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting.
Distribution
Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution at steady state (Vd,ss) was 683 L, and the apparent volume of distribution at steady state (Vd,ss/F) was approximately 10000 L.
Metabolism
Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minoextent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8

Ibrutinib binds covalently and irreversibly to Cys-481 near the BTK active site and inhibits the enzymatic activity with a half maximal inhibitory concentration (IC50) of 0.5 nM. The binding site of Bruton's tyrosine kinase remained fully occupied by ibrutinib (≥90% occupancy) for at least 24 hours in subjects treated with ibrutinib doses of ≥ 2.5mg/kg/day (≥ 175mg/day for average weight of 70kg. Although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post-dosing. Therefore, 560 mg/day is adequate to achieve exposures yielding full BTK active-site occupancy in most patients.

2.2.3 Clinical activity and Safety of ibrutinib

Ibrutinib was tested in a phase I, multicenter, open-label, dose escalation study in patients with recurrent NHL.(14) The objectives included studying the safety profile of ibrutinib, identifying the maximum tolerated dose (MTD) and optimal dosing schedule, and characterizing efficacy, pharmacokinetics, and pharmacodynamics. A minimum of 6 subjects per cohort received 1 of 5 escalating dose levels of ibrutinib between 1.25 and 12.5 mg/kg for 28 consecutive days in a 35-day cycle. There was a pre-specified objective of escalating 3 dose levels above that which achieved full BTK occupancy based on the fluorescent probe assay.

A total of 66 patients were evaluated in this study. Two additional cohorts received a continuous ibrutinib dose of 8.3 mg/kg without a 7-day rest and a fixed continuous dose of 560 mg/day. Full BTK occupancy was achieved with doses ≥2.5 mg/kg/day. A dose of 12.5 mg/kg/day was the highest dose cohort evaluated. There were 2 dose-limiting toxicities (DLTs) (Grade 2 neutropenia [2.5 mg/kg/day] and Grade 3 hypersensitivity [8.3 mg/kg/day]) in separate cohorts. The maximum tolerated dose (MTD) of ibrutinib in subjects with B-cell malignancies was not established in this study. Five of 15 subjects with DLBCL (33%) achieved objective responses, 2 CRs and 3 partial responses (PRs). The median

time on treatment was 8 weeks (range: 2 to 98 weeks). Median PFS was 2.5 months (range: 0.7 to 4.6 months) and the median follow-up time was 3.5 months (range: 0.8 to 22.5 months).

A subsequent phase I/II, multicenter, open-label, and single-arm study in subjects with rel/ref DLBCL was performed. (15)In order to determine whether ibrutinib had subtype specificity subjects enrolled were retrospectively analyzed into cohorts by subtype, either activated B-cell like (ABC) versus germinal B-cell like (GCB). Subtype analysis was performed by gene expression profiling (GEP). In this study all subjects received a starting dose of ibrutinib at 560 mg/day. The objectives of this study included the determining the safety of this dosing regimen and an assessment of efficacy of ibrutinib in DLBCL. Eighty subjects were enrolled and evaluable for response. The overall response rate (ORR) was 25% (20/80 subjects). In the ABC subtype, ORR was 37% (14/38 subjects; Only 1 PR (5%) was observed in the 20 patients retrospectively determined to be of GCB subtypes. Thus, while the 2 subgroups were retrospectively assigned, ibrutinib may be less active in rel/ref DLBCL, GCB subtype.

The most common adverse reactions (>=25%) in pts with B cell malignancies (MCL, CLL, WM) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection and rash.

2.3 Rationale for combination of Umbralisib and Ibrutinib

B-cell lymphomagenesis is known to be a result of aberrant signaling through the B-cell receptor (BCR). Several models have highlighted specific checkpoints that appear to be regulators of downstream signal propagation leading to abnormal nuclear transcription within the lymphocyte leading to either anti-apoptosis or a proliferative advantage.(5) A better understanding of the BCR signaling pathway has led to several small molecule inhibitors entering clinical practice as single agents. As described above, umbralisib and ibrutinib have shown safety and activity in DLBCL. Also important is the significant lack of evidence for cumulative toxicity as single agents to date. For umbralisib it has been postulated that the novel structure unlike other PI3K inhibitors has led to its lack of a significant toxicity profile making it a pairable novel oral agent. [redacted]. We propose that attacking the aberrant BCR signaling pathway at separate nodes may be an important mechanism to overcome the chemorefractory DLBCL regardless of cell of origin.

Alterations in single agent safety profiles can arise after an established MTD and often lessen the enthusiasm for such novel combinations and again question the durability of a continuous use paradigm. Nevertheless, combinations of oral novel-novel agents continue to emerge.(16) However, an example of unforeseen toxicities was highlighted in a recent report with lenalidomide, idelalisib (PI3-K inhibitor), and rituximab in patients with relapsed/refractory CLL and indolent NHL.(17) A sepsis-like syndrome was reported in 4 patients and resulted in stopping of these early phase studies without achieving a maximal tolerated dose (MTD).

It is well established dogma that a MTD is the objective in phase I studies. However, this only reports dose limiting toxicities during the initial cycle of therapy when further cumulative toxicities may be seen in subsequent cycles that limits the utility of a regimen. Therefore, in paradigms were long-term safety and tolerability is paramount and furthermore needed to balance with objective responses, a phase IIa study can be employed to not only provide this tolerability signal or cumulative toxicity events (CTEs), but be informative for future studies that lead to appropriately powered and better informed phase II or phase III studies.

As discussed above the phase I/Ib study (NCT #02006485) with ublituximab and umbralisib in rel/ref CLL and NHL continues to accrue. An amendment to this protocol allowed for the addition of ibrutinib at 560 mg daily to UTX (fixed at 900 mg) in addition to increasing doses of umbralisib. To date, safety data on umbralisib is notable for no episodes of hepatotoxicity reported with umbralisib as a single agent or in combination with ublituximab (doublet), or with ibrutinib (triplet).(10, 16, 18) In the 12 rel/ref DLBCL patients treated with umbralisib and UTX whom were eligible for response 5 patients had obtained a response and two had a PET/CT confirmed complete responses. Sixteen patients have been enrolled into the triplet regimen without a DLT in the NHL cohorts. The 800 mg dose level of umbralisib has been enrolled and completed without a DLT. Early responses have been seen in multiple NHL subtypes.

Given the safety of the umbralisib as a single agent, in the doublet and the triplet cohorts in combination with the early efficacy signal reported we propose to further explore the safety and tolerability of an all oral regimen of ibrutinib and umbralisib in patients with rel/ref DLBCL who have relapsed post-transplant or have been determined to be ineligible or unsuitable for transplant at the full doses of umbralisib (800 mg) and Ibrutinib (560 mg) in a single center open label phase IIa study.

Section 3.0 Eligibility Criteria:

3.1 Inclusion Criteria

1. Histologically confirmed Diffuse Large B-cell Lymphoma (DLBCL) or transformed DLBCL
2. Disease status defined as:
    a. Patients with relapsed or refractory DLBCL that has relapsed post-transplant or that has been determined to be ineligible or unsuitable for transplant. Patients must have received at least one prior systemic therapy.
3. Patients must have measurable (≥ 1.5 cm) or evaluable disease. Baseline measurements and evaluations must be obtained within 21 days of registration to the study. Abnormal PET scans will not constitute evaluable disease, unless verified by CT scan or other appropriate imaging. Measurable disease must have at least one objective measurable disease parameter. A clearly defined, bi-dimensionally measurable defect or mass measuring at least 1.5 cm in diameter on a CT scan will constitute measurable disease. Proof of lymphoma in the liver is required by a confirmation biopsy. Skin lesions can be used as measurable disease provided bi-dimensional measurements are possible.
4. Adequate organ system function, defined as follows:
    a. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
        i. By automated or manual review, whichever is greatest
    b. Platelets ≥100 x 10^9/L:
        i. *Unless due to bone marrow infiltration then eligible if platelets > 50* x 10^9/L*)*
    c. Total bilirubin ≤ 1.5 x upper normal limit if documented hepatic involvement with lymphoma, or ≤ 5 x upper normal limit if history of Gilbert's Disease.
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if documented liver involvement
    e. Creatinine ≤2.0 mg/dL OR calculated creatinine clearance ≥50 mL/min (as calculated by the Cockcroft-Gault method, Appendix B)
5. ECOG performance status ≤2 or expected survival duration of > 2 months (Appendix C)
6. Patients must be ≥19 years of age (the age of consent in Nebraska)
7. Ability to swallow and retain oral medication
8. Women must not be pregnant or breast-feeding due to teratogenic effects of therapy.
    a. All female patients of child-bearing potential must have a negative serum pregnancy test within 2 weeks prior to treatment to rule out pregnancy
    b. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
9. Male and female patients of reproductive potential must agree to follow accepted birth control measures throughout the study period and for 30 days after the last dose of either study drug for females and 3 months after the last dose of study drug for males.
10. Patient must be able to adhere to the study visit schedule and other protocol requirements.

11. Patient must be aware of the neoplastic nature of his/her disease and willingly sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.
12. No serious disease or condition that, in the opinion of the investigator, would compromise the patient's ability to participate in the study

3.2 Exclusion Criteria

1. Currently receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, and surgery and/or tumor embolization) or any investigational drug within 7 days of Cycle 1/Day 1, 14 days of Cycle 1/Day 1 for limited palliative radiation, and/or five half-live of an oral therapy.
    a. Corticosteroid therapy started at least 7 days prior to initiation of treatment (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted). Topical or inhaled corticosteroids are permitted.
2. Major surgery or a wound that has not fully healed within 4 weeks of enrollment.
3. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
4. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon.
5. Vaccinated with live, attenuated vaccines within 4 weeks of enrollment.
6. Autologous hematologic stem cell transplant within 3 months of study entry.
7. Allogeneic hematologic stem cell transplant within 12 months of study entry.
8. Active graft versus-host disease and must not be on immunosuppression.
9. Wide field radiotherapy within 28 days of Cycle 1/Day 1 or active side effects of such therapy
10. Active Hepatitis B (HBV) or C (HCV) infection (negative serology required excluding those with are seropositive due to prior vaccination) and/or known history of human immunodeficiency virus (HIV)
11. Primary central nervous system involvement only
12. Require treatment with strong CYP3A inhibitors
13. Known history of drug-induced liver injury, alcoholic liver disease, primary biliary cirrhosis, ongoing extra-hepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension
14. Any life-threatening illness, severe and/or uncontrolled medical condition, or organ system dysfunction, laboratory abnormality, psychiatric illness or other condition which, in the Investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, put the study outcomes at undue risk or affect their participation in the study such as:
    a. Symptomatic, or history of documented congestive heart failure New York Heart Association (NYHA) functional classification III-IV (NYHA, Appendix D)
    b. QTc >470 msec (unless related to pacemaker) on EKG within 21 days of initiation of treatment
    c. Angina not well-controlled by medication
    d. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting within 6 months prior to enrollment
15. Prior malignancies within the past 1 years with exception of adequately treated basal cell, squamous cell skin cancer, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Grade 6 or less with stable PSA levels.
16. Women who are pregnant or breastfeeding. Women who agree to stop breastfeeding would be eligible
17. Known hypersensitivity to either study drug (umbralisib or Ibrutinib)

NOTE:
All questions regarding eligibility for **UNMC potential subjects** should be directed to the PI at 402-559-7164.

NOTE: The eligibility checklist (Appendix E) may be used as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician. The eligibility checklist must be accompanied by all other source documents that evidence the subject's eligibility (i.e., dictation, pathology, radiology, laboratory, etc.)

Section 4.0 Registration Procedure:

All patients, with relapsed or refractory DLBCL that has relapsed post-transplant or that has been determined to be ineligible or unsuitable for transplant referred to The Nebraska Medical Center (TNMC), University of Nebraska Medical Center (UNMC), Bellevue Medical Center (BMC), and Village Point Cancer Center may be eligible for this trial.

Screening eligibility based on standard clinical care will be performed by the treating physician at the time of encounter. On initial presentation, a history and physical examination are performed, laboratory data obtained, and performance status is assessed. Imaging studies obtained include PET and a high-resolution multi-detector computed tomography (CT) of the chest, abdomen and pelvis. Further imaging studies will be obtained as clinically indicated. Pathology material must be reviewed, and a diagnosis of DLBCL confirmed by UNMC pathology department (retrospective). The patient's primary oncologist will make the decision as to screened eligibility of the candidate based on the eligibility criteria listed above, prior to offering consent.

If the patient is screened as potentially eligible, he/she will then be offered the option to participate. An informed consent will be signed by the patient after thorough review of the study is completed by the physician and his/her designee.

Some insurance carrier's may decline to cover the costs of usual medical care if the patient is participating in a clinical trial. The patient will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The patient can then decide if they wish to participate.

4.1 Eligibility Verification/Registration

Before subjects are registered to the study, an eligibility checklist (Appendix E) must be completed to verify the subject meets the eligibility criteria and may be used as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician. The eligibility check list will be maintained in the study file.

Date of Enrollment: Defined as the date of the start of study treatment / first study related intervention.

Study personnel from UNMC will provide the UNMC Fred & Pamela Buffett Cancer Center PRMS office (ZIP 6805) a copy of the signed and dated consent form for each UNMC subject enrolled in the protocol within 24 hours that includes the following information:

- Protocol Number
- Patient Identification: Patient's name UNMC/NMC medical record number
- Patient demographics: gender, birth date (mm/dd/yyyy), race, ethnicity,
- New CTRP reporting requirements: Patient zip code/country (if not USA) and primary method of payment information

4.2 Pathology Requirements

Pathological materials are to be submitted and reviewed at UNMC confirming a diagnosis of DLBCL or transformed DLBCL.

4.3 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a consented patient does not receive any assigned protocol treatment, baseline data will still be collected and must be submitted according to the instructions in the protocol. Document the reason for not starting protocol treatment on one of the baseline forms.

Section 5.0 Treatment Plan of Research Design:

This is a single-center Phase IIa study evaluating the safety and tolerability of umbralisib and Ibrutinib as well as the response and event free survival of this regimen in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). There will be 3 treatment groups given a maximum of one year (12 months) of therapy.

5.1 Pre-treatment Evaluations Standard of Care (SOC)

Within 21 days prior to the Date of Enrollment, date of the start of study treatment / first study related intervention (unless otherwise specified below). No tests or procedures are conducted solely for the purposes of research to determine subject eligibility.

- History and physical
- Informed Consent
- CBC, diff, platelets, CMET, LDH
- Hepatitis B (HBV) or C (HCV) serology
- Serum pregnancy test (if applicable) **within 14 days** of first study-related treatment date.
- Height and weight
- Vital signs, including blood pressure
- Performance Status
- EKG
- PET/CT baseline radiologic evaluation; NOTE for f/u if a Deauville 3 (CR) is achieved then CT chest, abdomen and pelvis with contrast may be used. Further PET/CT scans are optional at the investigators discretion.
- Mandatory research peripheral blood (20 mL) for cell free DNA assessment and T-cell characterization will be collected in an EDTA tube pretreatment (day of biopsy or initiation of treatment), day 8, 1 month (+/- 3 days) and 10mL at subsequent radiographic response assessments, after cycle 2, 4, 6, 9, and 12. (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion with collection of a research blood sample only if feasible. Should the patient consent any leftover peripheral blood collected for research will be stored at UNMC for future IHC and DNA unspecified research use.
-
- Optional Research Samples (Appendix G):
    - Should the patient consent, 3 additional optional lymph node biopsies for molecular profiling will be obtained at days 0 (pre-treatment; core biopsy), day 8 (FNA) and end of treatment (progressive disease, toxicity, or end of study—1 year; core biopsy) to evaluate the baseline characteristics and dynamic shifts in mutational landscape, transcriptional signatures and intracellular signaling cascades in primary tumor cells as well as assessment of comparative serologic response to radiographic assessments of response.

Specimens submitted, by patients who consent to the additional specimen collection, will be processed to maximize their utility for future unspecified research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA. Specimens will be archived with appropriate safeguards to ensure an efficient system for the prompt linkage and retrieval of the stored samples with the subject's study records.

Specimens from patients who consented to allow their specimens to be used for future IRB, TG Therapeutics, and Janssen Scientific LLC approved research studies, including residuals from the currently defined research studies, will be retained in an UNMC-designated central repository. If the patient agrees to let the samples be kept for future research, the samples will be kept until they are used up or destroyed. Most future research studies will focus on cancer, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer's disease. This may also include research on inherited traits. All future IRB, TG Therapeutics, and Janssen Scientific LLC approved research studies will be conducted in accordance with the requirements set forth in the UNMC Human Tissue Use and Transfer Policy (policy #8013).

5.2 Treatment Grouping and Dosing

Medicare qualifying research related combination chemotherapy:

Stratification will be performed on a 1:1:1 basis to Group A, B or C by willingness to consent to optional biopsies. The first 3 patients will be directly enrolled into cohort C regardless of decision to be included in the optional biopsy portion of the study.

Group A (consented to optional biopsies; 6 patients): umbralisib 800 mg PO daily on Days 1-8; then umbralisib 800 mg oral daily and Ibrutinib 560 mg oral daily

Group B (consented to optional biopsies; 6 patients): Ibrutinib 560 mg PO daily Days 1-8; then umbralisib 800 mg PO daily and Ibrutinib 560 mg PO daily

Group C (deferred consent to optional biopsies or consented to optional biopsies; 12 patients): umbralisib 800 mg PO daily and Ibrutinib 560 mg PO daily

All subjects will receive a maximum of 52 weeks of oral (self-administered) therapy. To provide a means of ensuring oral routes of medication adherence of patients while participating in a clinical trial **Appendix F** "Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure (V 1.0 11-25-2013)" will be followed.

No routine prophylactic antiemetics or pre-medications should be given outside of protocol requirements. However, these medications may be administered for symptoms when they occur, and may be given prophylactically afterwards. Appropriate anti-emetic regimens should be based on the recommendations made by the NCCN guidelines (SOC). http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf

5.2.1 Guidelines for Administration of umbralisib

- *Method of Administration:* Umbralisib 4 tablets each 200mg = 800mg will be administered orally once daily. **Umbralisib should be taken in the morning. (NOTE**: After cycle 2 if no CTE have been seen then the patient can have the option to take umbralisib and Ibrutinib dosing together at the same time of day).
- Umbralisib tablets should be swallowed whole with a full glass (approximately 8 ounces) of water. umbralisib tablets should NOT be crushed or chewed.
- *Potential Drug Interactions*: No Drug Interactions have been reported to date.
- *Pre-medications:* None

Umbralisib will be self-administered (by the patient). Tablets should be taken at approximately the same time each morning with food. Patients should be instructed to swallow the tablets whole and should not chew or crush them. If a dose of umbralisib is missed, it should be taken as soon as possible on the same day. If a dose is missed, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented. (Appendix F "Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure (V 1.0 11-25-2013)"

5.2.2 Guidelines for Administration of Ibrutinib

- *Method of Administration:* Ibrutinib 4 capsules each 140mg = 560mg will be administered orally once daily. **Ibrutinib should be taken in the evening. (NOTE:** After cycle 2 if no CTE have been seen then the patient can have the option to take umbralisib and Ibrutinib dosing together at the same time of day).
- Ibrutinib capsules should be swallowed whole with a full glass (approximately 8 ounces) of water. Ibrutinib capsules should not be opened, chewed or dissolved.
- *Potential Drug Interactions*: Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals

and antibiotics) consider interrupting ibrutinib therapy until the CYP3A inhibitor is no longer needed [see Drug Interactions (7.1)]. Reduce ibrutinib dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin) [see Drug Interactions (7.1)]. Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

- Also avoid grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A and can alter ibrutinib pharmacokinetics.
- For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of ibrutinib in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]
- *Pre-medications:* None

Ibrutinib will be self-administered (by the patient). Capsules should be taken at approximately the same time each evening with food. Patients should be instructed to swallow the capsules whole and should not chew, break or crush them. If a scheduled dose of Ibrutinib is missed it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose. If vomiting occurs, no attempt should be made to replace the vomited dose. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented. (Appendix F "Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure (V 1.0 11-25-2013)"

5.3 Supportive medications and procedures

The following treatments are prohibited while on clinical trial: other investigational drug treatments or study participation, radiation therapy (except as described in section 3.2 Exclusion Criteria #1), hormonal therapy for cancer, cancer immunotherapy or other biologic therapy excluding trial drugs.

- No glucocorticoids may be administered outside of protocol requirements for premedication or AE management, except low doses of steroids stabilized at $\leq$ 10 mg per day of prednisone or equivalent, and started at least 7 days prior to study entry.

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and supportive care concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Neutropenia: Granulocyte colony stimulating factor (G-CSF; filgrastim or pegfilgrastim) may be used during the course of the study at the investigator discretion. The drug(s) should be used at a dose/schedule specified in the package insert.

Antiemetics: Umbralisib and ibrutinib are considered to be of low emetogenic potential that may be adequately prevented with prochlorperazine. Other antiemetics may be used at the discretion of the treating physician if nausea and/or vomiting is not adequately controlled/prevented. Appropriate anti-emetic regimens should be based on the recommendations made by the NCCN guidelines (SOC). http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf

Tumor Lysis Syndrome: Subjects at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or institutional standards should be considered. Patients felt to be at risk for tumor lysis syndrome by the treating investigator will be monitored at least for the first 3 days of cycle 1 of therapy.

Pneumocystis Jiroveci Pneumonia (PCP) and Viral Infections: Prophylactic treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy should be considered. Recommended anti-viral prophylaxis is with Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent. Recommended PCP prophylaxis is with Dapsone 100 mg daily. Final choice of PCP and anti-viral prophylactic therapy is per investigator discretion. If PCP or anti-viral therapy is not

tolerated, alternate to a different PCP or anti-viral therapy, discontinue, or reduce dose/schedule as per investigator discretion.

Blood Product Support: Blood products should be utilized as clinically warranted and following institutional policies and recommendations.

5.4 Duration of therapy

In the absence of treatment delays due to adverse event(s), treatment should continue unless one of the following criteria applies:

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

5.5 Follow-up Evaluations Course Assessment Schedule

A cycle is 28 days of treatment with any oral agent regardless of group assignment. Response assessment will be done after cycles 2, 4, 6, 9, and 12 (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion.

We will continue to routinely monitor safety in regards to serious adverse events as well as for toxicity trends that may be of concern.

The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

Patients who discontinue therapy due to an adverse event should be followed until disease progression.

5. 6 Toxicity Assessments and Dose modifications

5.6.1 Definitions of Cumulative Toxicity Event (CTE)

For this protocol, cumulative toxicity event (CTE) will be defined as follows: an adverse event attributed (definitely, probably or possibly related) to the study treatment and meeting following criteria within cycles 1 to 4. AE grading and assignment of attribution require documentation by medical personnel who are directly involved in the clinical care of protocol subjects.

Toxicity	Definition
Hematologic	Either: 1. Grade 4 hematologic toxicities (attributed to either or both drugs) defined as: b. Grade 4 thrombocytopenia (platelets < 25 K/μL) c. Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5) 2. Grade 3 thrombocytopenia or neutropenia that results in a > 7 day delay in either drug.
Non-hematologic	Either: 1. ≥ Grade 3 as per NCI Common Terminology Criteria for Adverse Events v4.03* (attributed to either or both study drugs). 2. One week or greater delay in initiating any cycle day 1 due to continued drug-related toxicity.

*Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s) will be considered a CTE. Fatigue Grade >/= 3 considered to be due to treatment (definitely, probably, or possibly related) will be considered a CTE.

Patients should be assessed clinically for toxicity at each visit using the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) grading scale. The study will be terminated if a cumulative toxicity event (CTE) occurs in: ≥2/first 4; ≥4/first 8; or if more than 12 patients when the last (24th) evaluable patient has completed

cycle 4. If a patient has progression of disease or is removed from study not related to a CTE after completion of 2 cycles but less than 4 cycles the patients safety evaluation will be included, but noted appropriately. If the patient receives less than 2 cycles than the patient will not be included and noted, but will not be replaced.

Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.
Dose modification and or intervention with supportive care recommendations for umbralisib, and ibrutinib are provided below, however final discretion lies with the treating investigator in regards to more or less aggressive intervention, which specific investigational agent (or if both agents) needs to be reduced, and actual dose reductions, as well as the number of dose reductions.

5.6.2 Treatment Initiation/Continuation:

Starting a new cycle or continuing treatment after a CTE should be administered per protocol provided that:

- Absolute neutrophil count ≥ 1000/uL and platelet count ≥ 50,000/uL
- Recovered from grade 3-4 non-hematologic toxicity to grade 1 or baseline.
- Treatment may be delayed to recover from toxicity or per investigator discretion.
- No clinical or radiographic evidence of disease progression.

5.7 Dose modifications of Umbralisib and Ibrutinib for Adverse Reactions

If cytopenias are deemed related to the underlying disease rather than either umbralisib or ibrutinib, dose reductions are not required, or are per investigator discretion.

Worst CTCAE Grade Toxicity	Action to be Taken
Grade	Neutropenia Management
≤ Grade 1	No action required.
Grade 2	No action required; consider growth factor support.
Grade 3 or 4 first occurrence	Hold until < Grade 3. Consider growth factor support. Recheck in at least 1 week. Re-challenge at same dose level.
Grade 3 or 4 subsequent Occurrences	Hold until < Grade 3, or at patient's previous baseline. Recheck at least within 1 week. Doses are reduced 1 dose level.
Management of neutropenia is per institution guidelines and if in the opinion of treating investigator, are appropriate for patient care.	

Worst CTCAE Grade Toxicity	Action to be Taken
Grade	Thrombocytopenia Management
≤ Grade 1	No action required.
Grade 2	No action required.
Grade 3 or 4 1st Occurrence	Hold until < Grade 3, or at patient's previous baseline. Recheck at least within 1 week. Re-challenge at same dose level.
Grade 3 or 4 subsequent Occurrences	Hold until < Grade 3, or at patient's previous baseline. Recheck at least within 1 week. Doses are reduced 1 dose level.
Management of thrombocytopenia are per institution guidelines and if in the opinion of treating investigator, are appropriate for patient care.	

Patients who experience an adverse event that occurs after the CTE assessment window (cycle 1-6) will be allowed to delay umbralisib or ibrutinib dosing in order to recover from the toxicity. Patients may resume umbralisib and ibrutinib, provided that the toxicity has resolved to Grade ≤ 1 or baseline.

5.8 Non-Hematologic Toxicity

Grade 3 or 4 Non-Hematologic Toxicity

Worst CTCAE Grade Toxicity	Action to be Taken
Elevated Liver Enzymes	
Grade	Management
≤ Grade 1	No action required.
Grade 2	No action required.
Grade 3 or 4 1st Occurrence	Hold until < Grade 3, or at patient's previous baseline. Recheck at least within 1 week. Re-challenge at same dose level.
Grade 3 or 4 subsequent Occurrences	Hold until < Grade 3, or at patient's previous baseline. Recheck at least within 1 week. Doses are reduced 1 dose level.
Management of elevated liver enzymes are at the discretion of the investigator	

The dose reduction guidelines for other Grade 3-4 non-hematologic toxicities are shown below.

NON-HEMATOLOGIC	Action to be Taken
Renal	If serum creatinine >3 x baseline or >3 x ULN, hold dose until ≤ Grade 2.
Hepatic	For patients with mild liver impairment (Child-Pugh Class A) the recommended dose is 140mg daily (one capsule). Avoid the use of IMBRUVICA in pts with moderate or severe hepatic impairment (Child-Pugh Class B and C).
Cardiac	If a QTcF >500 msec has been demonstrated, hold dose: For all patients with a new QTcF >500 msec, occurring at any time during the study as identified by the investigator, an immediate evaluation of that ECG will be obtained and confirmed. All cardiac events should be treated as per the local standard of care and referral to a specialist if clinically indicated. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will occur after discussion between the Invest\gator. Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification

OTHER NON-HEMATOLOGIC	Recommended Action to be Taken
Grade 1 or 2	None
Grade 3 CTCAE	Hold dose until toxicity Grade ≤2. Reduce 1 dose level.
If toxicity remains grade 3 toxicity for longer than 2 weeks	Reduce by one dose level or discontinue treatment
If grade 3 toxicity lasts 2 weeks and resolves to ≤ Grade 2	Hold dose until toxicity Grade ≤2. Reduce 1 dose level
Recurrence of Grade 3 of toxicity	Consider reducing by one dose level
Grade 4 CTCAE	Hold dose until toxicity Grade ≤2, reduce 1 dose level.
Recurrence of Grade 4 toxicity	Reduce by one dose level or discontinue study drug

5.9 Dose Reduction Guidelines of Umbralisib and Ibrutinib

If a hematologic toxicity is deemed to be related to the study combination both drugs will be reduced. If a non-hematologic AE occurs and is felt to be related to only one of the study drug, this drug can be dose reduced alone.

Dose Modifications	Umbralisib	Ibrutinib	Day	Route
-1	600 mg	560mg	Day 1-28	orally
-2	400 mg	420mg	Day 1-28	orally
-3	200 mg	280mg	Day 1-28	orally

5.10 Assessments

5.10.1 Disease Assessment Schedule

A dedicated PET/CT Response assessment will be done after cycles 2, 4, 6, 9, and 12 (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion. If a PET/CT CR (Deauville 3 or less) is seen then a CT of chest, abdomen, and pelvis with contrast can be substituted.

A restaging bone marrow biopsy may be done if a staging bone marrow biopsy was previously positive or if symptoms suggest involvement.

Patients with stable disease after 6 cycles can continue treatment if the treating investigator feels the subject is deriving benefit. Patients with progressive disease (PD) at any time are off study and will discontinue study treatment.

Patients achieving PR/CR or stable disease that are felt by the investigator to be deriving a benefit may continue until disease progression or for a maximum of 12 cycles (52 weeks of any treatment).

5.10.2 Post Trial Assessments

Patients who go off study treatment at any time during the trial will be followed for 30 days after the last day of treatment. For all patients, drug-related SAEs and AEs will be followed until baseline or ≤ grade 1 levels. Patients who responded or maintained stable disease during the study will be followed for date of disease progression. Patients may refuse to participate in the post-trial assessments.

5.11 Biospecimens

5.11.1 Mandatory Human Biologic Materials

Pathology materials should be submitted and reviewed at UNMC confirming the diagnosis of DLBCL or transformed DLBCL.

Mandatory peripheral blood (20 mL) for cell free DNA assessment and peripheral mononuclear cells will be collected in an EDTA tube pretreatment (day of biopsy or initiation of treatment), day 8, 1 month (+/- 3 days) and 10 mL will be collected at subsequent radiographic response assessments, after cycle 2, 4, 6, 9, and 12. (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion with collection of a research blood sample only if feasible.

5.11.2 Somatic Mutations Affecting B-cell Receptor Signaling

Prior studies have identified somatic mutations in genes that regulate or modify signaling downstream from the B-cell receptor and toll-like receptor pathway, including CD79A, CD79B, CARD11, and MYD88. In addition, these mutations may be associated with the clinical response to Ibrutinib. To account for the potential influence of these mutations on response, they will be assessed from pre-treatment biopsy specimens by next generation sequencing. To achieve this, DNA will be extracted from tumor specimens, genome-wide next generation sequencing libraries constructed, and hybrid capture utilized to isolate 386 genes that are recurrently mutated in B-cell lymphoma, including those listed above.

5.11.3 Quantitative Assessment of Kinetics and Depth of Response

Tumor cells release DNA into the peripheral blood and it is detectable within the cell-free DNA (cfDNA) fraction isolated from plasma. Recent studies have shown that the burden of tumor specific cfDNA in the plasma correlates with metabolic tumor volume.(19, 20) In order to quantitatively assess the magnitude and kinetics of response and association with radiographic response we will employ cfDNA sequencing by isolating cfDNA from peripheral blood samples collected in a 20 ml EDTA tube pretreatment (day of biopsy or initiation of treatment), day 8, 1 month (+/- 3 days) and 10mL EDTA tube at subsequent radiographic response assessments, after cycle 2, 4, 6, 9, and 12. (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion with 10ml EDTA peripheral blood samples obtained ONLY IF FEASIBLE. We will create next-generation sequencing libraries, and performing hybrid capture for genes with identified mutations from the tumor biopsy specimen as well as immunoglobulin genes. (Appendix G Blood and Tissue Sample Processing and Shipping)

This will allow multiple tumor-specific genetic markers to be followed in the peripheral blood, and quantitative assessment of response to be calculated by the change in allelic fraction of somatic mutations.

5.11.4 Cell Signaling Characteristics

Malignant B-cells have unique intracellular signaling characteristics that vary between patients.(21) We will assess the basal level of signaling downstream from the B-cell receptor in pre-treatment biopsies using intracellular phospho-specific flow cytometry. Therein, tumor B-cells can be identified using surface markers and fixed and permeabilized cells interrogated using antibodies that are specific for activating phosphorylation markers on multiple proteins. Using fluorescent barcoding and 10-color multiplexing, we will assess the activity of proximal B-cell receptor signaling components (Lyn, Syk, Btk, Blnk, Plcg2), phosphoinositol-3-kinase signaling molecules (Akt, S6K) and downstream targets of casein kinase signaling (EIF4E, Myc)). This will provide a quantitative measure of the basal activation of these pathways within patient tumor biopsies prior to treatment. Optional lymph node biopsies will be obtained via US or computer tomography (CT) guided biopsy of accessible lymph nodes at day 0 (pre-treatment; core biopsy), day 8 (FNA) and end of treatment (progressive disease, toxicity, or end of study—1 year; core biopsy) so as to assess the change in signaling resulting from treatment. (Appendix G Blood and Tissue Sample Processing and Shipping)

5.11.5 Peripheral T-cell Characteristics

Ibrutinib and umbralisib have been described to have secondary targets of Itk and CK1ε, respectively [PMID.(22, 23) These molecules play a role in T-helper cell differentiation by promoting or inhibiting Th2 polarization, respectively. We will therefore monitor the change in T- cell characteristics using 10mL of peripheral blood in EDTA from pre-treatment and day 8 and 1-month. This will include the interrogation of cytokines (IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-6,

IL10, IL-13), phenotypic markers (CD3, CD4, CD25, CD45RO, CCR6, CCR7, CD27, CD127, CXCR3, HLA-DR, CD38) and intracellular transcription factors (FoxP3, T-bet, GATA3).

6.0 Measurement of Effect:

6.1 Response to therapy:

Response to therapy will be classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), early death, or not evaluable. Response to therapy will be determined after cycle 2, 4, 6, 9, and 12 (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion.

Patients with a global deterioration of health status requiring permanent discontinuation of study treatment (taken off study) without objective evidence of disease progression will be counted as progressive disease unless a prior CR or PR has been previously documented. Every effort should be made to document the objective progression even after discontinuation of treatment. Deaths will be counted as treatment failure.

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

CR can be achieved at any response evaluation of umbralisib and ibrutinib.

Definitions for clinical response for patients with lymphoma are from the Lugano Response Criteria for Malignant Lymphoma.(24) Lymph node measurements should be taken from CT or the CT portion of the PET/CT. Measurement of lymphadenopathy will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SDP). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable, such as diffuse infiltration of an organ such as the stomach, bone marrow, peripheral blood, liver, lungs, or bowel by lymphoma without a discrete mass would constitute assessable, but not measurable, disease (eg, Lymph node or tumor mass greater than 1.5 cm in at least one dimension by physical exam, splenic enlargement, if the spleen is palpable, at least 3 cm below the left costal margin) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

Response is based on PET/CT (Deauville 3 or less) or CT alone if CR is achieved by PET/CT.

Response criteria, modified from the Lugano response criteria. DLBCL is considered FDG avid.

Response Category	Definition	Nodal Masses	Spleen, liver	Bone Marrow
CR	Disappearance of all evidence of disease.	Mass of any size permitted if PET negative	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable	≥50% decrease in SPD of up to 6 largest dominant	≥50% decrease in SPD of nodules (for single nodule	Irrelevant if positive prior to therapy; cell type should be specified

	disease and no new sites	masses; no increase in size of other nodes **and** one or more PET positive at previously involved site	in greatest transverse diameter); no increase in size of liver or spleen	
SD	Failure to attain CR/PR or PD	PET positive at prior sites of disease and no new sites on CT or PET		
Relapse/ Progressive disease	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase from nadir in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node > 1 cm in short axis. The lesions referred to above are required to be PET positive.	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

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

6.2 Complete Response (CR):

6.2.1 Complete disappearance of all detectable clinical evidence of disease and definitely disease-related symptoms if present before therapy.

6.2.2 DLBCL is a FDG-avid lymphoma: when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

6.2.3 The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

6.2.4 If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be

adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

6.3 Criteria for Partial Response (PR). The designation of PR requires all of the following:

6.3.1 At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following:

- they should be clearly measurable in at least 2 perpendicular dimensions
- if possible they should be from disparate regions of the body
- they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

6.3.2 No increase should be observed in the size of other nodes, liver, or spleen.

6.3.3 Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

6.3.4 With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

6.3.5 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6.3.6 No new sites of disease should be observed.

6.3.7 For patients with PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

6.4 Criteria for Stable Disease (SD):

6.4.1 A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR (see above), but does not fulfill those for progressive disease (see below).

6.4.2 The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

6.5 **Relapsed Disease (after CR)/Progressive Disease (after PR, SD):**
Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

6.5.1 Appearance of any new lesion more than 1.5 cm in any axis during or after completion of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site

should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

6.5.2 At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

6.5.3 At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

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

7.0 STUDY PARAMETERS - Test Schedule for cycle 1-12

Cycle (C) = 28 days	Screening	Cycle 1			CTE Period Cycles 2-4	Cycle 5-12	End of Treatment[6]
Procedure \ Days (D)	21-0	Day 1 ± 3days	Day 8	Day 28	Day 1[7]	Day 1	
Informed consent	X						
Pathology confirmation of diagnosis of DLBCL or transformed DLBCL.	X						
Medical history	X						
Physical examination[1]	X	X	X		X	X	
Vital signs (pulse rate, BP, temperature)[1]	X	X			X	X	
ECOG performance status[1]	X	X			X	X	
Optional lymph node biopsy[8]		X	X				X
Mandatory Research peripheral blood samples [9]		X	X	X	X[9]	X[9]	X
EKG	X						
Serology: HCV, HBV[2]	X						
Umbralisib	Defined by Grouping (A,B,C)				Daily (1-28)	Daily (1-28)	
Ibrutinib	Defined by Grouping (A,B,C)				Daily (1-28)	Daily (1-28)	
Hematology[1]	X[7]	X	X		X	X	
Serum Chemistry[1]	X[7]	X	X		X	X	
Lactate dehydrogenase (LDH)	X		X		X	X	
Serum Pregnancy test[3]	X						
Radiographic Tumor Evaluation[4]	X				X[5]	X[5]	

[1] Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have +/- 3 day window in cycle 1 and +/- 7 day window during cycles 2-12.

[2] To confirm negative HBV and HCV

[3] For women of child bearing potential completed within 14 days prior to Day 1 of Cycle 1

[4]Tumor evaluation must include a PET/CT; if a Deauville 3 (CR) is achieved then CT chest, abdomen and pelvis with contrast may be used. Further PET/CT scans are optional at the investigators discretion. All tumor evaluations have +/- 7 day window.

[5] Response evaluation will occur after cycle 2, 4, 6, 9, and 12 (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion.

[6] End of study will be the next visit following a cycle after study drug was administered. If a patient has completed 12 cycles of treatment without evidence of PD the patient will be monitor for relapse or progression at the discretion of the treating investigator. Follow up after 1 year of therapy will be per institutional guidelines. Patient can be taken off study to proceed to allogeneic stem cell transplant. Patients will be censored for EFS and DOR, but will be available for OS assessment.

[7] The study will be terminated if a cumulative toxicity event (CTE) occurs in: ≥2/first 4; ≥4/first 8; or if more than 12 patients when the last (24th) evaluable patients has completed cycle 4. If a patient has progression of disease or is removed from study not related to a CTE after completion of 2 cycles but less than 4 cycles the patient's safety evaluation will be included, but noted appropriately. If less than 2 cycles than the patient will not be included and noted, but will not be replaced. The stopping rule would be appropriately adjusted if this were to occur.

[8] Optional biopsies obtained via US or CT guided biopsy of accessible lymph node: Day 0 (pre-treatment; core biopsy), day 8 (fine needle aspiration) and end of treatment (progressive disease or end of study treatment—1 year; core biopsy). At the discretion of the treating investigator, patient on non-coumadin based anticoagulation should have anticoagulant held for biopsy.

[9] Mandatory research peripheral blood samples will be collected in a 20 ml EDTA tube pretreatment (day of biopsy or initiation of treatment; (+/- 3 days)), day 8 (+/- 3 days), 1 month (+/- 3 days) and 10 mL at subsequent radiographic response assessments, after cycle 2, 4, 6, 9, and 12. (+/- 7 days). After Month 12, efficacy assessments should occur at the investigators discretion with 10mL EDTA peripheral blood samples obtained ONLY IF FEASIBLE.]

Section 8.0 Drug Formulation and Procurement:

8.1 Umbralisib

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 (micronized): 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:	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.

8.2 Ibrutinib

Classification:	Irreversible inhibitor of Bruton's Tyrosine Kinase
Formulation:	See Investigator Brochure
Mode of action:	Irreversibility inhibits activity of Bruton's Tyrosine Kinase
How Supplied:	Ibrutinib: 140 mg capsules (hard gelatin capsule). Refer to the ibrutinib Investigator's Brochure for a list of excipients.
Storage:	Store at 20○ C to 25○ C
Route:	Oral
Availability:	Ibrutinib is available from Janssen Scientific Affairs, LLC.

8.3 Administration of Umbralisib and ibrutinib

At each visit, patients will be dispensed sufficient umbralisib and ibrutinib drug supplies until the next visit. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented.

Umbralisib and ibrutinib will be self-administered by the patients. Umbralisib (4 200mg tablets = 800mg) and ibrutinib (4 140mg tablets = 560mg) will be administered orally once daily. Umbralisib should be taken in the morning. Ibrutinib should be taken in the evening. (NOTE: After cycle 2 if no CTE have been seen then the patient can have the option to take umbralisib and Ibrutinib dosing together at the same time of day.)

Umbralisib and ibrutinib tablets should be swallowed whole with a full glass (approximately 8 ounces) of water. Umbralisib tablets should NOT be crushed/opened or chewed. Ibrutinib capsules should not be opened, broken or chewed.

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The following adverse events have been reported to occur in patients receiving similar PI3K inhibitors: increased ALT/AST, skin rash, enteritis, and pneumonia.

Refer to the current Investigator Brochure for details of the risks associated with the use of umbralisib, and instructions on how to manage patients.

Prohibitions and restrictions for ibrutinib:
The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any planned surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For planned minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure, or at the discretion of the investigator.

8.5 Ibrutinib Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The most common side effects, occurring in at least 1 of every 5 patients (≥ 20%), have been:

- Increase in frequency of loose or watery stools (Diarrhea)
- Muscle and bone pain (Musculoskeletal pain)
- Nausea
- Low white blood cell count (cells that help fight infection) (Neutropenia)
- Rash
- Bruises

Side effects that have been seen in at least 1 of every 10 (≥ 10%) patients include:

- Fever (Pyrexia)
- Low platelet count (cells that help blood to clot) (Thrombocytopenia)
- Common cold (Upper Respiratory Tract Infection)
- Pneumonia
- Constipation
- Swelling of the hands or feet (Oedema peripheral)
- Muscle spasms
- Vomiting
- Joint aches (Arthralgia)
- Sores in mouth (Stomatitis)
- Headache
- High Blood pressure (Hypertension)
- Skin infection
- Sinus infection (Sinusitis)

Side effects that have been seen in at least 1 of every 100 (≥ 1%) patients include:

- Dizziness
- Urinary tract infection
- Noses bleed (Epistaxis)
- Increased level of uric acid in the blood (Hyperuricemia)
- Small red or purple spots caused by bleeding under the skin (Petechiae)
- Abnormal heart rhythm (Atrial fibrillation)
- Non-melanoma skin cancer
    - Type of non melanoma skin cancer (Basal cell carcinoma)
    - Type of non melanoma skin cancer (Squamous cell carcinoma)
- Blurry vision (Vision blurred)
- Low white blood cell counts with fever (Febrile neutropenia)
- Severe infection throughout the body (Sepsis)
- Redness of the skin (Erythema)
- Increase in white blood cell counts (Leukocytosis)
- Breaking of the nails (Onychoclasis)
- Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
- Increase in lymphocyte count (Lymphocytosis)

Side effects that have been seen in at least 1 of every 1000 (<1%) patients include:

- Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures. (Tumor lysis syndrome)
- Itchy rash (Urticaria)
- Bleeding around the brain (Subdural hematoma)
- Swollen face, lip, mouth, tongue or throat (Angioedema)
- High WBC count with abnormal clumping that can lead to bleeding (Leukostasis syndrome)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- Liver failure (Hepatic failure)

Hemorrhage
Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib.

The mechanism for the bleeding events is not well understood.

Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Monitor patients for fever and infections and evaluate promptly.

A rare and usually fatal viral disease in the brain, Progressive Multifocal Leukoencephalopathy (PML), has been reported in patients treated with ibrutinib in combination with rituximab and in patients who were previously treated with rituximab.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with ibrutinib. Monitor complete blood counts monthly.

Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of ibrutinib treatment and dose modification.

Hypertension

Hypertension (range, 6 to 17%) has occurred in patients treated with ibrutinib with a median time to onset of 4.5 months (rang, 0.03 to 18.40 months). Monitor patients for new onset hypertension or hypertension that is not

adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatments as appropriate.

Second Primary Malignancies

Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to11 %).

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

Embryo-Fetal Toxicity

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Allergic reactions

Serious allergic reactions to ibrutinib, including rash, difficulty breathing, wheezing, sudden low blood pressure with light-headedness, swelling around the mouth, throat or eyes, a racing heartbeat, and/or sweating may occur.

Rash

A maculopapular rash (flat, red areas on the skin with small bumps) has been commonly reported in patients treated with ibrutinib alone or in combination with other drugs. Most rashes are mild to moderate in severity and begin 2 to 3 weeks or longer after starting ibrutinib.

There have been rare reports of severe skin reactions (known as severe cutaneous adverse reaction or “SCAR”, involving more than 50% of the body) or rash with blisters and peeling skin, which may include open ulcers or sores in the mouth and other areas of the body (Stevens - Johnson syndrome). These skin rashes could be life-threatening.

Lymphocytosis and leukostasis

Lymphocytosis is an increase in the number of lymphocytes, a type of white blood cell, in your blood. This may occur in the first few weeks of treatment and one should not assume that this increase in white blood cells means that the disease is worsening. This increase may last for several weeks to months. Increased number of white blood cells in the bloodstream may alter blood flow resulting in bleeding or clotting (leukostasis). Isolated cases of these events have been reported in patients treated with ibrutinib.

Liver Failure

Rare cases of liver failure have been reported in patients treated with ibrutinib.

Interstitial lung disease

Lung abnormalities not associated with infections (e.g, bacteria, viruses, fungi) have been reported in patients treated with ibrutinib

Interference with other drugs

Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way the body processes ibrutinib. This interference could cause the amount of ibrutinib in the body to be higher or lower than expected. It is also possible that taking the study drug with regular medications or supplements, including fish oil, Vitamin E, or other vitamins, may change how the regular medications, or regular supplements, work. It is very important that grapefruit juice and Seville oranges be avoided.

9.0 Toxicity and Adverse Event Reporting Guidelines

The reporting is only for TGR 1202 and Ibrutinib "study medications," until 30 days after last administration of study medication.

NOTE: Problems related to insurance coverage for UNMC potential subjects or enrolled subjects will be reported to the IRB as they are encountered.

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

All patients will be closely followed for toxicity from the time of informed consent until 30 days after last administration of study medication. Adverse event and serious adverse events will be followed until baseline or ≤ grade 1 levels. Toxicity will be assessed using the revised NCI CTCAE version 4.02.

All adverse events will be followed to a satisfactory conclusion. Serious adverse events should be followed until resolution, death, or until no further improvement is reasonably expected. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC DSMC.

In addition to complying with all applicable regulatory reporting laws and regulations, all serious adverse events and toxicities will be reported to the University of Nebraska Medical Center, Institutional Review Board (IRB), participating sites own IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

Definitions:

Adverse Event
An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.,* the surgery

is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

An adverse event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 5.0, Treatment Plan) and/or if the investigator considers them to be adverse events. In general, if a laboratory abnormality or change in vital sign is associated with a specific diagnosis that is being reported concurrently as an adverse event (e.g. elevated creatinine with renal failure or sinus tachycardia in febrile neutropenia) the findings that support the diagnosis do not need to be reported as separate adverse events unless the investigator feels it is appropriate.

Treatment-emergent Adverse Event

Treatment-emergent adverse event is defined as any adverse event with onset or worsening from the time that the first dose of study drug is administered until 30 days after the final dose of study drug is administered.

Unexpected Adverse Event

An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the labeled event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Serious Adverse Event

A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Pregnancy

[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such 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. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.1 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC)

This protocol will adhere to all institutional guidelines for adverse event reporting. Adverse events will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTC-AE) version 4.02.

9.1.1 IRB REPORTING

All internal serious adverse events (AE) must be reported to the local IRB promptly per institutional policy [UNMC – through the electronic Research Support System(s) (RSS) mechanism] and in no case later than two (2) business days following PI notification that the event occurred *if* the principal investigator determines that conditions A, B, and C are met:

a. The AE is unexpected, *AND*
b. The AE is related to, or possibly related to, the drug, biologic, device, or other research intervention, *AND*
c. The AE is more than minor in nature which is defined as requiring treatment from a health professional.

All *unexpected*, internal, fatal AEs must be reported promptly to the local IRB per institutional policy [UNMC - through the electronic RSS mechanism], but no later than *24 hours* following PI notification that the event occurred. If documentation is still pending, the IRB office must be notified by a telephone call or e-mail.

All *expected*, internal, fatal AEs (i.e., due to progressive disease or which reflect a risk currently found in the consent form) must be reported to the local IRB per institutional policy [UNMC - through the electronic RSS system] no later than ten (10) business days following PI notification that the event occurred.
The UNMC RSS is accessed through a link on the UNMC IRB website (http://unmc.edu/irb).

9.1.2 FRED & PAMELA BUFFETT CANCER CENTER DATA AND SAFETY MONITORING COMMITTEE (DSMC) REPORTING

Per UNMC DSMC guidelines, the following must be reported:

- All adverse events ≥ grade 3 (expected or unexpected, regardless of attribution) will be reported to the University of Nebraska Medical Center, Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).
- All **serious** adverse events will be fully reported and reviewed by the University of Nebraska Medical Center, Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).
    - The principal investigator is responsible for submitting a copy of the UNMC SAE Assessment Form along with a blinded copy of any related patient source documents
    - If additional information about the SAE is still being collected a preliminary report should be filed to the DSMC within seven (7) business days with final reporting when additional information is available.

Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.

Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.

Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.

Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.

Definitely related: There occurrence and timing of the AE are clearly attributable to the study treatment.

Severity Grade of AE. The severity of events reported on the AE case report form will be determined by the principal investigator according the NCI Common Toxicity Criteria (CTC version 4.02).

AEs will be collected from the time the subject signs the consent form and ending 30 days following the final chemotherapy. All AEs will be followed until resolution or a cause is identified. Prescription medication taken to relieve symptoms of the AE will be recorded in addition to the outcome.

AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the 30 days after the final chemotherapy.

Copies of the SAE report will be submitted to the IRB as indicated in Section 9.1.1.

Detailed policy and procedures for this section may be reviewed at: http://www.unmc.edu/cancercenter/clinical/prms.html

9.1.3 **FOOD AND DRUG ADMINISTRATION (FDA) REPORTING**

It is the responsibility of the UNMC sponsor-investigator, Matthew Lunning, D.O., to submit to the FDA IND Safety Reports in accordance with 21 CFR 312.32. The SAE will be submitted to FDA if the PI determines 21CRF312.32 criteria are met.

SAEs not meeting expedited criteria will be made available to FDA by the sponsor-investigator via the annual report.

The investigator will utilize the FDA MedWatch Form (Appendix H) for the reporting of serious adverse events and follow up information to those events. The form can be found at the following URL: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Additionally, serious adverse events will be reported to the IRB, SRC, Audit Committee and the Data Safety Monitoring Committee by the Investigator as described further within Section 9.0.

9.1.4 Janssen Interventional Investigator Initiated Study Requirements for Safety Data Collection and Reporting

Overview

As the sponsor of the Study, PRINCIPAL INVESTIGATOR shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

UNMC and PRINCIPAL INVESTIGATOR will provide safety information to the Janssen on adverse events, special situations including pregnancies and product quality complaints as defined within this Section.

Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this section will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: Ibrutinib (Imbruvica)

Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Adverse Events of Special Interest

Adverse events of special interest are events that the Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Major Hemorrhage
  Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.
- Intracranial Hemorrhage
  Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.
- Other Malignancies
  In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)

- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., auto injector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.imbruvica.com/hcp/?utm_source=google&utm_medium=cpc&utm_campaign=Imbruvica&utm_term=imbruvica&utm_content=ibrutinib-+Exact|mkwid|ssjPpM0Gh_dc|pcrid|39412243694

Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from Janssen Scientific Affairs, LLC and TG Therapeutics perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to the Janssen Scientific Affairs LLC and TG Therapeutics within **24 hours of becoming aware of the event.**

Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC and TG Therapeutics by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse

Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at the Janssen's request.

Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen

All adverse events and special situations whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The PRINCIPAL INVESTIGATOR) will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs and TG Therapeutics in accordance with Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, to Janssen Scientific Affairs, LLC using Janssen's Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE or special situation is required.

- The PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method listed below within **24 hours of such report or correspondence being sent to applicable health authorities.**

Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC and TG Therapeutics Y according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to Janssen according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen.

Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs.

9.2 Auditing

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) will review this protocol on at least an annual basis.

This study will undergo audit on at least a quarterly basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html.

Section 10.0 Statistical Considerations

The phase IIa portion will further assess the safety and tolerability and allow a preliminary assessment of the efficacy of the novel combination to provide background for an appropriately powered phase II study. We plan to accrue 24 patients into the phase IIa portion at a micronized dose of 800 mg of umbralisib and 560 mg of ibrutinib. The assessment of toxicity and efficacy will be performed within the entire cohort. To consecutively monitor the safety primary endpoint in the phase IIa portion, we will employ a sequential probability stopping rule for the predefined portion of cycles 1-4. This stopping rule specifies that the study will be terminated if a cumulative toxicity event (CTE) occurs in: ≥2/first 4; ≥4/first 8; or if more than 12 patients when the last (24^{th}) evaluable patient has completed the trial have any CTE. This rule has the following stopping probability:

True toxicity rate	5%	10%	15%	20%	25%	30%	35%	40%	50%
Stopping prob.	0.000	0.000	0.001	0.004	0.016	0.056	0.118	0.243	0.632

A CTE is defined as:

- Grade ≥ 3 non-hematologic (attributed to either or both study drugs)
- Grade 4 hematologic toxicities (attributed to either or both drugs) defined as:
  - Grade 4 thrombocytopenia (platelets < 25 K/μL)
  - Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5)
- Grade 3 thrombocytopenia or neutropenia that results in a > 7 day delay in either drug.
- One week or greater delay in initiating any cycle day 1 due to continued drug-related toxicity.

If a patient has progression of disease or is removed from study not related to a CTE after completion of 2 cycles but less than 4 cycles the patient's safety evaluation will be included, but noted appropriately. If less than 2 cycles than the patient will not be included and noted, but will not be replaced. The stopping rule would be appropriately adjusted if this were to occur.

An efficacy-stopping rule is also in place for the combination. After testing the combination on 12 patients, the trial will be terminated if </= 1 patients respond. If the trial goes on to the second stage and not discontinued due to the CTE stopping rules prior to, a total of 24 patients will be studied. If the total number responding is less than or equal to five, the regimen will be rejected. This follows a Simon two-stage design for efficacy following a minimax design with the following parameters: overall response rate for a poor regimen of 0.01, overall response rate for a good regimen of 0.31, a type I error of 0.20 and power of 80%.

Efficacy measures which will be determined include ORR, TTR, DOR, and PFS. ORR is defined as the percentage of patients achieving a best response of CR/CR, PR at any disease assessment time point. TTR is defined as the time or number of cycles between study registration and documentation of first response (CR/Cru, or PR). DOR is defined as the time or number of cycles between documentation of first response and progression, change of therapy, death, or date of last contact (if still alive without progression). PFS is defined as the time between study registration and documented progression or death if no progression was observed.

11.0 RECORDS TO BE KEPT

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms. See attached Data forms. Source documents which support data entered must be provided for centralized compliance monitoring. Serious adverse events, when noted, will be recorded on site via the standard serious adverse effects form.

11.1 Quality assurance

Complete records must be maintained in a research chart on each patient treated on the protocol. These records should include primary documentation (e.g., lab. report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given & reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (x-ray, scan, lab reports, dated notes on measurements & clinical assessment, as appropriate).

11.2 Medidata Rave 5.6 Electronic Data Capturing (EDC) System

The UNMC Fred & Pamela Buffett Cancer Center (NCI-designated cancer center) is a participant in the National Cancer Institute Cancer Biomedical Informatics Grid (CaBIG™) initiative.

The NCI purchased software license for cancer centers use of Medidata Rave 5.6 a web-based EDC application for managing clinical trial data across multiple cancer clinical trials. Data will be stored electronically for this study on the Rave secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Rave logo.

Medidata Rave 5.6 provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Medidata Rave 5.6 through a secure connection and must provide a valid username, password, and database ID. De-identified research data will be shared with the NCI and the CaBIG community. This data may be made available to the public at large.

RAVE Builder Contact Information
University of Nebraska Medical Center
Fred & Pamela Buffett Cancer Center
Att: Eugene “Gene” Sehi, M.S., CCRP
986805 Nebraska Medical Center
Omaha, NE 68198-6805
FAX: (402) 559-5669 Ph: (402) 559-8514
Email: esehi@unmc.edu

12.0 PATIENT CONSENT

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population

Patients are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material

Pathology material (as stated in Section 5) must be reviewed, and the diagnosis confirmed by University of Nebraska Medical Center pathology department (retrospectively) as outlined in the protocol.

12.4 Recruitment and Informed Consent

Patients with a history of relapsed or refractory DLBCL for whom this therapy would be appropriate will be available for recruitment. These patients will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed below.

National Library of Medicine - http://clinicaltrials.gov (NCT02874404)
National Cancer Institute - http://www.cancer.gov (NCI-2016-01082)

12.5 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent

If the patient chooses to be a participant in this study, informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld.

The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects

It is hoped that the use of protocol therapy in this patient population may result in tumor shrinkage or stabilization of disease.

12.10 Potential Benefits to Society.

Information obtained from this study may help patients by Identifying safety and tolerability of umbralisib and ibrutinib.

12.11 Potential Risks

Use of umbralisib and ibrutinib is associated with numerous potential risks. Combinations of novel targeted therapies are considered to be a valid treatment option for patients with advanced malignancies. It is believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment that might consist of other chemotherapy drugs given alone or in combination.

12.12 Therapeutic Alternatives

If patients choose not to participate in this study they may elect to receive standard salvage therapy as per their primary oncologist, which may include other chemotherapy drugs given alone or in combination.

12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of chemotherapy agents, the risk is considered to be acceptable in the setting of cancer.

12.14 Consent Form Documents

No information will be purposely withheld from the patients. The consent document used in this study will include the adult consent document. (See attached consent form)

Section 13.0 References

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Section 14.0 Data Collection Forms

Attached.

Appendix A:
Use of ibrutinib with other CYP3A inhibitors or inducers (per ibrutinib USPI)

CYP3A Inhibitors:
In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased Cmax and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng· hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics treatment for 7 days or less e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin)) consider interrupting ibrutinib therapy until the CYP3A inhibitor is no longer needed. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin). Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

CYP3A Inducers:
Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreased ibrutinib Cmax and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

Appendix B:
Cockroft-Gault Creatinine Clearance Calculation

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows:

CrCl (ml/min) = (140-age) (actual wt in kg) divided by 72 x serum creatinine (mg/dl)

For females use 85% of calculated CrCl value.

Appendix C
Performance Status Criteria

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

Appendix D
NEW YORK HEART ASSOCIATION (NYHA) HEART DISEASE CLASSIFICATION

Class	Definition
I.	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, or dyspnea.
II.	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, or dyspnea.
III.	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, or dyspnea.
IV.	Unable to carry on any physical activity without symptoms. Symptoms are present even at rest. If any physical activity is undertaken, symptoms are increased.

Appendix E
Eligibility Checklist

Date Completed:	Institution:	Patient ID#:	Checklist Version #3.0 Dated: 14Jul2017
IRB# 345-15 Title: : A Single-center Phase IIa Study Evaluating the Safety and Tolerability of umbralisib and Ibrutinib in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma: A Trial of the Lymphoma Precision Medicine Laboratory Reference #: PI: Mathew Lunning, MD		Waiver #:	
Gender: [ ] M [ ] F	Race: [ ] White[ ] Black [ ] Hispanic [ ] Asian [ ] Native American [ ] Other [ ] Unknown		
Zip Code/country (if not USA):	Primary method of payment information:		

Inclusion Criteria: **Response should be YES**	Yes	No	N/A
1. Histologically confirmed Diffuse Large B-cell Lymphoma (DLBCL) or transformed DLBCL	[ ]	[ ]	1.
2.			
2. Disease status defined as Patients with relapsed or refractory DLBCL that has relapsed post-transplant or that has been determined to be ineligible or unsuitable for transplant. Patients must have received at least one prior systemic therapy.	[ ]	[ ]	[ ]
3. Patients must have measurable (≥ 1.5 cm) or evaluable disease. Baseline measurements and evaluations must be obtained within 21 days of registration to the study. Abnormal PET scans will not constitute evaluable disease, unless verified by CT scan or other appropriate imaging. Measurable disease must have at least one objective measurable disease parameter. A clearly defined, bi-dimensionally measurable defect or mass measuring at least 1.5 cm in diameter on a CT scan will constitute measurable disease. Proof of lymphoma in the liver is required by a confirmation biopsy. Skin lesions can be used as measurable disease provided bi-dimensional measurements are possible	[ ]	[ ]	

4. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L i. By automated or manual review, whichever is greatest b. Platelets ≥100 x 10^9/L: i. *Unless due to bone marrow infiltration then eligible if platelets > 50* x 10^9/L*)* c. Total bilirubin ≤ 1.5 x upper normal limit if documented hepatic involvement with lymphoma, or ≤ 5 x upper normal limit if history of Gilbert's Disease. d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if documented liver involvement e. Creatinine ≤2.0 mg/dL OR calculated creatinine clearance ≥50 mL/min (as calculated by the Cockcroft-Gault method, Appendix B)	[ ] [ ]
5. ECOG performance status ≤2 or expected survival duration of > 2 months (Appendix C)	[ ] [ ]
6. Patients must be ≥19 years of age (the age of consent in Nebraska)	[ ] [ ]
7. Ability to swallow and retain oral medication	[ ] [ ]
8. Women must not be pregnant or breast-feeding due to teratogenic effects of therapy All female patients of child-bearing potential must have a negative serum pregnancy test within 2 weeks prior to treatment to rule out pregnancy Pregnancy testing is not required for post-menopausal or surgically sterilized women	[ ] [ ] [ ]
9. Male and female patients of reproductive potential must agree to follow accepted birth control measures throughout the study period and for 30 days after the last dose of either study drug for females and 3 months after the last dose of study drug for males	[ ] [ ]
10. Patient must be able to adhere to the study visit schedule and other protocol requirements	[ ] [ ] [ ]
11. Patient must be aware of the neoplastic nature of his/her disease and willingly sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study	[ ] [ ]

12. No serious disease or condition that, in the opinion of the investigator, would compromise the patient's ability to participate in the study	[ ] [ ]
Exclusion Criteria: **Response should be NO**	Yes No N/A
1. Currently receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, and surgery and/or tumor embolization) or any investigational drug within 7 days of Cycle 1/Day 1, 14 days of Cycle 1/Day 1 for limited palliative radiation, and/or five half-live of an oral therapy Corticosteroid therapy started at least 7 days prior to initiation of treatment (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted). Topical or inhaled corticosteroids are permitted	[ ] [ ]
2. Major surgery or a wound that has not fully healed within 4 weeks of enrollment	[ ] [ ]
3. History of stroke or intracranial hemorrhage within 6 months prior to enrollment	[ ] [ ]
4. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon)	[ ] [ ]
5. Vaccinated with live, attenuated vaccines within 4 weeks of enrollment	[ ] [ ]
6. Autologous hematologic stem cell transplant within 3 months of study entry	[ ] [ ]
7. Allogeneic hematologic stem cell transplant within 12 months of study entry	[ ] [ ]
8. Active graft versus-host disease and must not be on immunosuppression	[ ] [ ]
9. Wide field radiotherapy within 28 days of Cycle 1/Day 1 or active side effects of such therapy	[ ] [ ]

10. Active Hepatitis B (HBV) or C (HCV) infection (negative serology required excluding those with are seropositive due to prior vaccination) and/or known history of human immunodeficiency virus (HIV)	[ ] [ ]
11. Primary central nervous system involvement only	[ ] [ ]
12. Require treatment with strong CYP3A inhibitors	[ ] [ ]
13.Known history of drug-induced liver injury, alcoholic liver disease, primary biliary cirrhosis, ongoing extra-hepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension	[ ] [ ]
14. Any life-threatening illness, severe and/or uncontrolled medical condition, or organ system dysfunction, laboratory abnormality, psychiatric illness or other condition which, in the Investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, put the study outcomes at undue risk or affect their participation in the study such as: a. Symptomatic, or history of documented congestive heart failure New York Heart Association (NYHA) functional classification III-IV (NYHA, Appendix D) b. QTc >470 msec (unless related to pacemaker) on EKG within 21 days of initiation of treatment c. Angina not well-controlled by medication d. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting within 6 months prior to enrollment	[ ] [ ]
15. Prior malignancies within the past 1 years with exception of adequately treated basal cell, squamous cell skin cancer, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Grade 6 or less with stable PSA levels	[ ] [ ]
16. Women who are pregnant or breastfeeding. Women who agree to stop breastfeeding would be eligible	[ ] [ ]
17. Known hypersensitivity to either study drug (umbralisib or Ibrutinib)	[ ] [ ]

NOTE: All questions regarding eligibility for potential subjects should be directed to the PI at 402-559-5166.

Eligibility: [ ] Patient satisfies all criteria
[ ] Patient not formally eligible, but admitted to this study because (state reason):

Patient Initials: _____MR or Study ID#_____DOB _____

ELIGIBILITY reviewed and confirmed.
Consenting/Treating Investigator Signature _____Date_____
Printed Name of Consenting/Treating Investigator: _____

Appendix F
Oral, Sublingual, and/or Buccal Route
Medication Adherence Standard Procedure
(V 1.0 11-25-2013)

PURPOSE

To provide a means of ensuring oral, sublingual and/or buccal routes of medication adherence to patients while participating in a clinical trial.

1. A physician's order will be completed by study patients or representative for oral, sublingual and/or buccal administration per IRB approved protocol.
2. To ensure the consistent and safe administration of medications not given under the direct supervision of study staff (at home), there will be a "Medication Information Sheet" and a calendar to document times of drug administration.
3. To record medication adherence Study staff will document results of medication reconciliation and or medication return in the patient's chart.
4. Maintain documentation of medications returned or sent to investigational pharmacy for destruction (if applicable).

PROCEDURE

1. Protocol specific information regarding the individual medication(s) should be listed on the form "Medication Information Sheet" and given to the patient at the start of the study and throughout treatment if necessary to help ensure adherence. (See Form A)
2. Name, dose and route of each medication should be listed under 'How to take your Medication' on the "Medication Information Sheet".
3. Patients will be given a monthly "Medication Calendar". The calendar will have a place for the patient to record the time that the medication(s) were taken. (See Form B for example)
4. The research nurse will review the patient's "Medication Calendar" for adherence to the study regimen for oral medication administration. Adherence will be noted in the patient's chart. Medication reconciliation will be done and if there is medication to be returned/destroyed it will be sent to the Nebraska Medical Center Investigational Pharmacist for return/destruction in accordance to the Nebraska Medical Center Destruction of Investigational product, Policy #4.860.

Name:
MR:
Study ID:

Medication Information Sheet (Form A)

IRB# 345-16 Title of protocol: A Single-center Phase IIa Study Evaluating the Safety and Tolerability of umbralisib (formerly known as TGR-1202) and Ibrutinib in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma: A Trial of the Lymphoma Precision Medicine Laboratory

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You have been enrolled into the following Dosing Group _____.
How to take your medication:
Group A: You will take umbralisib 800mg (4 tablets) Day 1-8
Starting day 9, you will take both umbralisib 800mg (4 tablets) and Ibrutinib 560mg (4 capsules) by mouth once a day with a full 8 ounce glass of water until your treating physician tells you to stop. Follow your Medication Calendar that is provided to record your dosing.

Group B: You will take Ibrutinib 560mg (4 capsules) Day 1-8
Starting day 9, you will take both umbralisib 800mg (4 tablets) and Ibrutinib 560 mg (4 capsules) by mouth once a day with a full 8ounce glass of water until your treating physician tells you to stop. Follow your Medication Calendar that is provided to record your dosing.

Group C: You will take both umbralisib 800mg (4 tablets) and Ibrutinib 560 mg (4 capsules) by mouth once a day with a full 8ounce glass of water until your treating physician tells you to stop. Follow your Medication Calendar that is provided to record your dosing.

- **Umbralisib should be taken in the AM. (NOTE**: After cycle 2 if no side effects have been seen you can have the option to take umbralisib and Ibrutinib dosing together at the same time of day.)
- **Ibrutinib should be taken in the evening. (NOTE:** After cycle 2 if no side effects have been seen you can have the option to take umbralisib and Ibrutinib dosing together at the same time of day.)

Things to know about your medication:

1. The dose of the study medications will remain the same during your entire treatment, unless your doctor informs you of a change.
2. If your doctor modifies the dose of either medication for any reason, please record the change on your Medication Calendar (Form B).
3. You should take your medications at the same time each day with food.
4. You should avoid grapefruit and Seville oranges (Known as "Chinese Bitter Orange", bitter orange, sour orange, bigarade orange, or marmalade orange. The Seville orange variety is used in the production of marmalade/cooking) during treatment, as these can alter the absorption of the medications.
5. You should swallow the tablets and capsules as a whole, **do not** chew or crush them.
6. If you miss a dose of your medications, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. If a dose is missed make sure to mark it on your Medication Calendar (Form B).
7. If vomiting occurs, no attempt should be made to replace the vomited doses.

Your Doctor is: _____Contact Phone # _____
Your Research Nurse is: _____Contact Phone # _____
After hours, nights, weekends and holidays please call 402-559-5600 and ask for the Oncologist on call.

Medication Diary (Form B) *Template*

(Form B)

Name:
MR:
Study ID:

345-16: Medication Calendar

Group A

Your TGR-1202 Dose is_____. Take_____tablets each day.

Your Ibrutinib Dose is_____. Take_____ capsules each day.

Day	Date			Time TGR 1202 Tablets taken		Time Ibrutinib Capsules taken		Notes
	Month	Day	Year	AM	PM	AM	PM	
1						Do not take Ibrutinib during the first 8 days.		
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(Form B)

Name:
MR:
Study ID:

345-16: Medication Calendar

Group B

Your TGR-1202 Dose is _____. Take_____ tablets each day.

Your Ibrutinib Dose is _____. Take _____capsules each day.

Day	Date Month	Day	Year	Time TGR 1202 Tablets taken AM	PM	Time Ibrutinib Capsules taken AM	PM	Notes
1				Do not take TGR 1202 during the first 8 days.				
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(Form B)

Name:
MR:
Study ID:

345-16: Medication Calendar

Group C

Your TGR-1202 Dose is_____ . Take_____tablets each day.

Your Ibrutinib Dose is_____. Take _____capsules each day.

Day	Date			Time TGR 1202 Tablets taken		Time Ibrutinib Capsules taken		Notes
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
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(Form B)

Name:
MR:
Study ID:

345-16: Medication Calendar

Cycle _____ (Any Group)

Your TGR-1202 Dose is_____ . Take _____ tablets each day.

Your Ibrutinib Dose is_____ . Take _____ capsules each day.

Day	Date			Time TGR 1202 Tablets taken		Time Ibrutinib Capsules taken		Notes
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
4								
5								
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Appendix G
Blood and Tissue Sample Processing and Shipping

Description of Sample Collection:
No therapeutic intervention will be undertaken and the results of these studies will not have any influence on the medical management of the subjects.

Lymph Node Biopsy Guidelines:
Day 1 – pretreatment and END OF TREATMENT or Progression
CORE NEEDLE BIOPSY
STANDARD path review
Plus 2 cores requested for research.
Per Dr McBride, it is standard for them to use an 18 gauge. Sample size is approx. 2cm per each core.

Day 8 – cycle 1 of treatment
FINE NEEDLE ASPIRATE
Sample ONLY FOR RESEARCH.
No path review needed.
Collect sample per the IR standard. Per Dr. McBride, it is standard to use a 22g or 25g needle. They determine what size is best, based on the patient. They will provide aspirate per their standard process. Typically, four passes for collection of FNA.

Facility	Sample	Contact Person(s)	Date and Time Points
UNMC Designated Repository Laboratory	Optional Lymph Node Pathology material: Lymph node biopsies obtained via US guided biopsy of accessible lymph node at day 0 (pre-treatment; core biopsy), day 8 (fine needle aspiration) and end of treatment (progressive disease or end of study treatment—1 year; core biopsy)	Keenan Hartert Phone: 402-559 7921Email: keenan.hartert@unmc.edu	☐ Baseline day 0 (pre-treatment; core biopsy) Date: ___/___/____ ☐ Day 8 (fine needle aspiration) Date: ___/___/____ ☐ End of treatment (progressive disease or end of study treatment—1 year; core biopsy) Date: ___/___/____
UNMC Designated Repository Laboratory	Mandatory Research blood specimen: 20 ml EDTA tube pretreatment (day of biopsy or initiation of treatment), day 8, 1 month (+/- 3 days) and 10ml EDTA at subsequent radiographic response assessments, after cycle 2, 4, 6, 9, and 12. (+/- 7	Keenan HartertPhone: 402-559-7921 Email: keenan.hartert@unmc.edu Location: UNMC Designated Repository Laboratory F&PBCC, 4th floor, Room 379	☐ Baseline Blood Sample (pretreatment = day of biopsy or initiation of treatment) Date: ___/___/____ ☐ Day 8 Blood Sample Date: ___/___/____

	days). After Month 12, efficacy assessments should occur at the investigators discretion with 10ml EDTA peripheral blood samples obtained ONLY IF FEASIBLE. Additional ☐ Optional: **Please Check the box if patient consented** to the storing of any leftover peripheral blood for future unspecified research use)		☐ 1 month (+/- 3 days) Blood Sample Date: ___/___/____ Page 1 of 2 ☐ Re-staging Blood Sample after cycle 2 (+/- 7 days). Date: ___/___/____ ☐ Re-staging Blood Sample after cycle 4 (+/- 7 days). Date: ___/___/____ ☐ Re-staging Blood Sample after cycle 6 (+/- 7 days). Date: ___/___/____ ☐ Re-staging Blood Sample after cycle 9 (+/- 7 days). Date: ___/___/____ ☐ Re-staging Blood Sample after cycle 12 (+/- 7 days) Date: ___/___/____ **After Month 12, efficacy assessments should occur at the investigators discretion peripheral blood samples obtained ONLY IF FEASIBLE.** ☐ Re-staging Blood Sample Date: ___/___/____ ☐ Re-staging Blood Sample Date: ___/___/____ ☐ Re-staging Blood Sample Date: ___/___/____

			☐ Re-staging Blood Sample Date: ___/___/____

Appendix H
FDA MEDWATCH form

Available on-line at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf