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NCT: NCT02268851

TG Therapeutics, Inc. Protocol #: *TGR-IB-105*

Title: A Multi-center Phase I/Ib Study Evaluating the Efficacy and Safety of the Novel PI3k Delta Inhibitor TGR-1202 in Combination with Ibrutinib in Patients with Select B-Cell Malignancies.

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Agents: TGR-1202 (umbralisib) TG Therapeutics, Inc.
Ibrutinib, Commercial

IND #: 123439
IND Sponsor: Matthew Davids, MD

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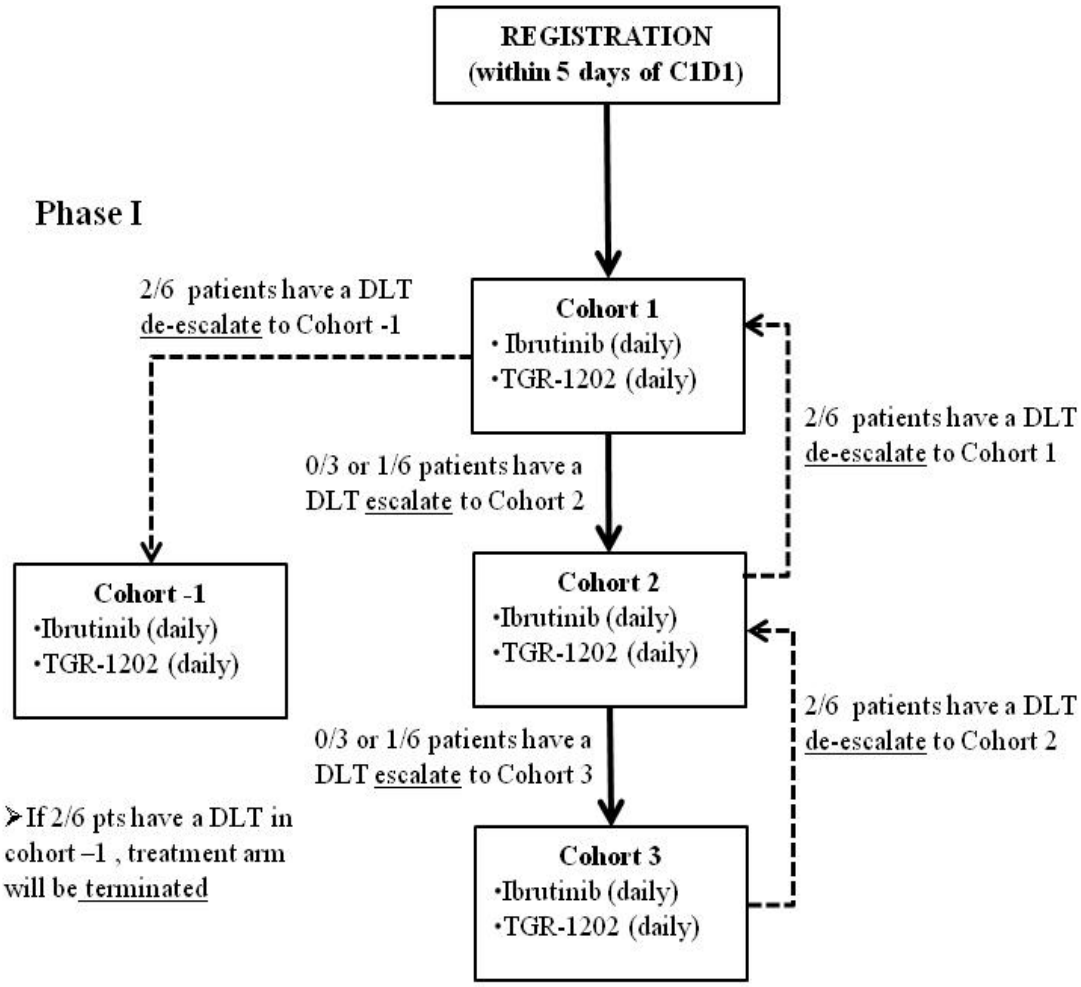
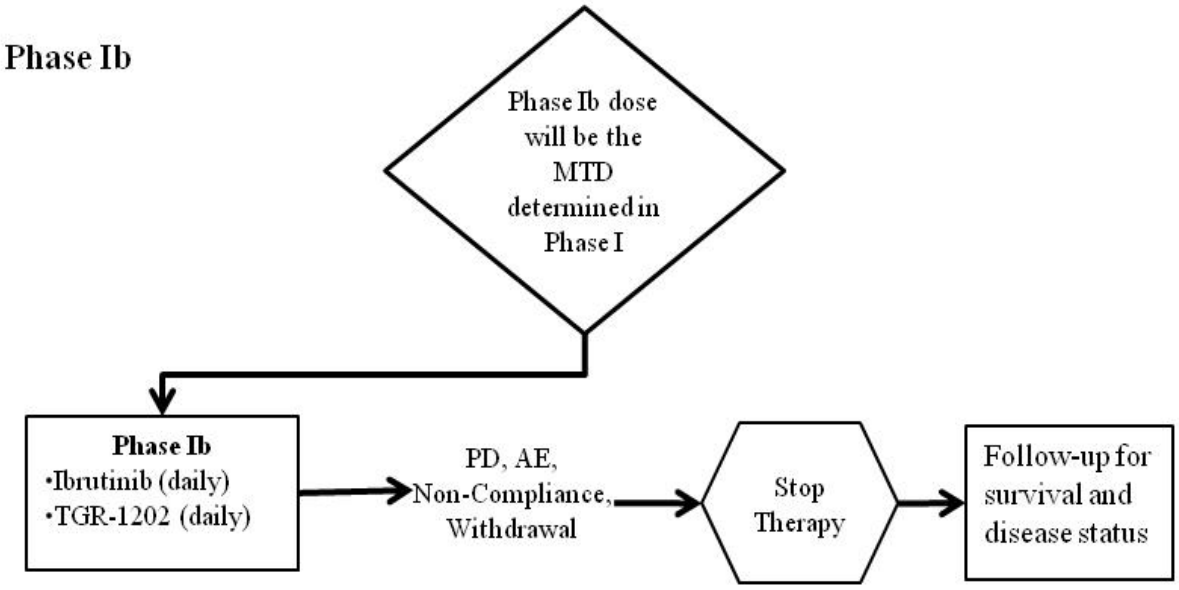
SCHEMA


REGISTRATION
(within 5 days of C1D1)
Phase I
2/6 patients have a DLT
de-escalate to Cohort -1
Cohort 1
• Ibrutinib (daily)
•TGR-1202 (daily)
2/6 patients have a DLT
de-escalate to Cohort 1
0/3 or 1/6 patients have a
DLT escalate to Cohort 2
Cohort -1
•Ibrutinib (daily)
•TGR-1202 (daily)
Cohort 2
•Ibrutinib (daily)
•TGR-1202 (daily)
2/6 patients have a DLT
de-escalate to Cohort 2
0/3 or 1/6 patients have a
DLT escalate to Cohort 3
➢If 2/6 pts have a DLT in
cohort –1 , treatment arm
will be terminated
Cohort 3
•Ibrutinib (daily)
•TGR-1202 (daily)

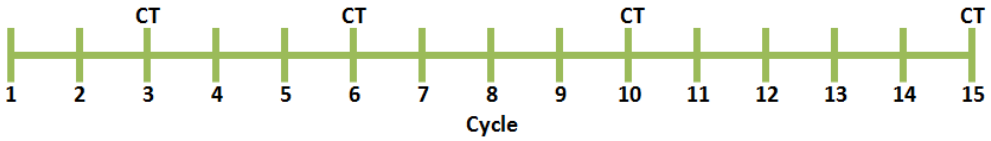

Phase Ib
Phase Ib dose
will be the
MTD
determined in
Phase I
Phase Ib
•Ibrutinib (daily)
•TGR-1202 (daily)
PD, AE,
Non-Compliance,
Withdrawal
Stop
Therapy
Follow-up for
survival and
disease status

SYNOPSIS

Study Rationale	TGR-1202 is a highly specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The delta isoform of PI3K is highly expressed in malignant lymphocytes, where it serves as a key node in the B cell receptor (BCR) signaling pathway, thereby making this an attractive target for selective inhibition of malignant B cells. TGR-1202 is currently in a Phase I dose escalation trial, evaluating sequentially higher single agent doses until a maximum tolerated dose (MTD) is determined. Ibrutinib is an inhibitor of Bruton's Tyrosine Kinase (BTK), another key enzyme found at a different point in the BCR pathway, which has been found to be critical for B-cell proliferation and survival (Byrd et al., 2013). Ibrutinib is approved for the treatment of patients with relapsed or refractory Mantle Cell Lymphoma (MCL) and Chronic Lymphocytic Leukemia (CLL). Although ibrutinib monotherapy is a promising therapy for relapsed CLL and MCL, not all patients respond to ibrutinib therapy, and among patients who initially do respond, complete responses have been rare, and resistance mechanisms have already been described, such as the C481S binding site mutations recently reported in CLL. Dual inhibition of both PI3K-delta and BTK holds the promise of both more complete BCR pathway inhibition and also the reduced likelihood of developing treatment resistance. The purpose of this study is to explore the safety and efficacy of the PI3K-delta inhibitor TGR-1202 in combination with the BTK inhibitor ibrutinib, two novel, oral, once daily, targeted agents in patients with select B-cell lymphoid malignancies.
Products	TGR-1202 is a highly specific and orally available PI3K delta (δ) inhibitor available for this study in 200 mg tablets, supplied by TG Therapeutics, Inc. Ibrutinib is an orally available inhibitor of Bruton's Tyrosine Kinase (BTK) commercially available in 140 mg capsules from Pharmacyclics, Inc. / Janssen Pharmaceuticals.
Study Objectives	**Primary Objectives** • To determine the maximum tolerated dose (MTD) of TGR-1202 when used in combination with ibrutinib in patients with relapsed or refractory CLL or MCL. • To evaluate the safety and determine any dose limiting toxicities (DLTs) of TGR-1202 in combination with ibrutinib in patients with relapsed or refractory CLL or MCL. **Secondary Objectives** • To preliminarily characterize the efficacy of TGR-1202 at its MTD in combination with ibrutinib by determining the overall response rate (ORR) defined as the sum of the complete response (CR) and partial response (PR) rate, as well as to determine the rate of nodal response with lymphocytosis (nPR), progression-free survival (PFS), and duration of response (DOR).

	Exploratory Objectives • To assess whether apoptotic priming as determined by BH3 profiling and pharmacodynamic response as determined by phospho-flow are predictive of clinical response.
Efficacy Endpoints	**<u>Efficacy Endpoints:</u>** Overall response rate, defined as sum of CR and PR rates. Responses will be determined according to response criteria as follows: • MCL: International Working Group (Cheson et. al 2007; Revised Response Criteria for Malignant Lymphoma, [Appendix A]); • CLL: International Workshop for Chronic Lymphocytic Leukemia (IW-CLL) Response Criteria (Hallek et al. 2008 [Appendix B]) as modified by Cheson et al., 2012.
Safety Endpoints	AEs will be evaluated during the treatment period and for 30 days following discontinuation from the study using CTCAE v4.0. The DLT observation period will be the first cycle (28 days).

Study Design	Up to 30 subjects per disease group (MCL and CLL/SLL), including a potential 12 qualified patients who will have completed the Phase Ib dose confirmation part of the study, may be enrolled. "Up to" is written because the Phase Ib can potentially stop early.
	
	Phase I Dose Confirmation:
	• 3 + 3 design using Cycle 1 DLTs for both CLL/SLL and MCL patients, conducted independently in parallel, with a minimum of 3 patients in a cohort, as follows:
	  o MCL: 3-6 patients at cohort 1
	  o CLL/SLL: 3- 6 patients at cohort 1
	• If <u>no</u> DLTs are reported among the initial in 3 patients in Cohort 1, the dose level will be considered safely cleared, and dose escalation may proceed to Cohort 2. If no DLTs are reported in 3 patients in Cohort 2, the dose will be considered safe for Cohort 3. If no DLT's are reported among the initial in 3 patients in Cohort 3, the Phase Ib part of the study will open.
	• If 1 DLT is reported in either Cohort 1, 2 or 3, an additional 3 patients will be enrolled. If no additional DLTs are reported ($\leq$ 1/6 pts), then dose escalation will continue to the next cohort or Phase Ib (if in Cohort 3 already).
	• If at least two patients experience a DLT in either Cohort 1 (MCL or CLL/SLL), the combination dose will be considered above the maximum tolerated dose and the dose Cohort -1 will enroll 3-6 patients. The same DLT rules will apply for Cohort -1 except if 2/6 patients experience a DLT in Cohort -1 the study will end for that respective group. If at least two

	patients experience a DLT in Cohort 2 or 3, the next highest dose level which has cleared DLT evaluation will be considered the dose for the Phase Ib part of the study. **<u>Phase Ib:</u>** Once the dose has been confirmed separately for MCL and CLL/SLL patients, the Phase Ib will open and enroll up to 12 additional patients. The efficacy evaluation will include the 6 patients from the Ph I cohort dose for up to approximately 18 total patients evaluable for efficacy in each patient group (MCL & CLL/SLL).
Treatment Study Visits	**Each Cycle = 28 days** **<u>Cycle 1:</u>** • TGR-1202 (oral): Starting on Day 1 administered daily in the morning with food, preferably within 30 minutes of a meal • Ibrutinib (oral): Starting on Day 1 administered daily in the evening **<u>Cycles 2 and >:</u>** Daily treatment with both TGR-1202 and ibrutinib should continue. First efficacy assessment should be approximately 8 weeks (just prior to cycle 3) after Cycle 1/Day 1 (+/- 7 days) and approximately every 12 weeks thereafter (+/- 7 days) through cycle 12 following initiation of therapy (schema below).  After cycle 12, regular visits should occur every 3 cycles. After the Cycle 15 restaging, disease assessments should occur at least every 6 cycles (+/- 14 days) through cycle 36, at which point assessments can be done per investigator's discretion. After removal from study, patients should be followed for survival approximately every 3 months for up to 2 years
Baseline Lab Evaluation (Local Lab)	• CBC with differential • Serum chemistry • Serology to rule out active Hep B, C or HIV infection • Serum pregnancy test • FISH cytogenetic analysis • *IGHV* mutation status (CLL patients only- Test performed by Integrated Oncology- See correlatives section 9.1.2.3)
Instrumental Tests	• Computed tomography (CT) of the chest, abdomen, pelvis (and neck if palpable cervical adenopathy is present) at screening. Assessments should

<table>
<tr><td></td><td>occur C2D28, C5D28, C9D28, C14D28, then approximately every 6 cycles (+/-14 days) until Cycle 36. Disease assessments after Cycle 36 may be done at the investigator's discretion. After removal from study, patients should be followed for survival every 3 months for up to 2 years or until death, lost to follow up, or initiation of a new CLL/MCL directed therapy
• CT scan and bone marrow biopsy are mandatory for confirmation of a complete response.
• Any patient who achieves a clinical response may have CT scans reviewed and confirmed by independent assessment.</td></tr>
<tr><td>Dosing Regimen</td><td>As of June 2014, TGR-1202 continues to enroll patients in a single agent, Phase I dose escalation trial, which has evaluated doses as high as 1800 mg QD. TGR-1202 was subsequently reformulated for greater absorption, and the administration state changed from a fasting state to a fed state, with a dose of 400 mg projected to provide comparable plasma exposure to doses safely cleared in the single-agent study. Ibrutinib is an approved agent for MCL and for CLL/SLL, and is commercially available. TGR-1202 (TGR) and ibrutinib will be administered orally, once per day according to the schedule below. A 3+3 dose escalation design will be utilized to evaluate the dosing cohorts described below. Both the CLL and MCL cohorts will start at dose level 1.
Phase I (Dose Confirmation) – Cycle 1 Schedule
<table>
<tr><th>Dose Level</th><th>TGR Dose</th><th>Ibrutinib Dose MCL</th><th>Ibrutinib Dose CLL</th></tr>
<tr><td>1</td><td>400 mg</td><td>560 mg</td><td>420 mg</td></tr>
<tr><td>2</td><td>600 mg</td><td>560 mg</td><td>420 mg</td></tr>
<tr><td>3</td><td>800 mg</td><td>560 mg</td><td>420 mg</td></tr>
<tr><td colspan="4">If ≥ 2 DLT's in either Cohort 1, 3- 6 pts will enroll in Cohort -1 as follows:</td></tr>
<tr><td>-1</td><td>200 mg</td><td>560 mg</td><td>420 mg</td></tr>
<tr><td colspan="4">If ≥ 2 DLT's in a Cohort –1 treatment group, study will be terminated</td></tr>
</table>
Cycle 2 and >
Patients will continue daily administration of TGR-1202 + ibrutinib until progression or removal from study per investigator decision.
The sponsor representative and Principal Investigator will be in charge of reviewing safety data (SAE's / AE's) after the 3rd patient of each Phase I Cohort (or 6th patient, in the event a DLT occurs among the first 3 patients) completes Cycle 1. They will recommend whether or not it is possible to move into the Phase Ib portion for both the MCL and CLL disease groups independently as per the study design.

Phase Ib:
Once the dose in the Phase I has been confirmed for either the MCL or CLL patient groups, the Phase Ib part of the study will open. All subjects will be treated at the established cohort dose per the same administration schedule from</td></tr>
</table>

	the Phase I portion (TGR-1202 and ibrutinib administered on Day 1 of Cycle 1 at the doses noted above and continued daily). For all patients at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

Inclusion Criteria	• Confirmed diagnosis of Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL), or Small Lymphocytic Lymphoma (SLL)
	  ○ **MCL patients must have**:
	  ▪ At least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma
	  ▪ Received at least one prior standard therapy for MCL
	  ○ **CLL/SLL patients must have**:
	  ▪ Indication for treatment according to the 2008 IWCLL Criteria
	  ▪ Received at least one prior standard treatment regimen
	• Adequate organ system function, defined as follows:
	• Absolute neutrophil count (ANC) ≥ 500 / platelet count ≥ 30,000. (*Patients who have cytopenias due to significant bone marrow infiltration do not have to meet hematologic eligibility criteria. Significant bone marrow infiltration is defined as >50% involvement by CLL.)*
	• Total bilirubin ≤ 1.5 times the upper limit of normal (ULN), unless due to Gilbert's disease or hemolysis, then ≤ 3.0 times ULN.
	• Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.0 x ULN if no liver involvement or ≤ 4x the ULN if known liver involvement
	• Creatinine ≤ 2.5 mg/dL OR calculated creatinine clearance ≥ 50 mL/min (as calculated by the Cockcroft-Gault method)
	• ECOG performance status ≤ 2
	• Patients must be at least 18 years of age
	In the phase I portion, patients having received prior BTK inhibitors or prior PI3K inhibitors are eligible
	• Ability to swallow and retain oral medication
	• Female patients who are not of child-bearing potential and female patients of child-bearing potential who have a negative serum pregnancy test at study screening. A tubal ligation is sufficient documentation that a patient is not of childbearing potential.
	• Female patients of child-bearing potential, and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 30 days after the last dose of either study drug.
	• Willingness and ability to comply with trial and follow-up procedures, and give written informed consent

Exclusion Criteria	• Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) within 3 weeks of Cycle 1/Day 1, with the following

	exceptions: o Patients currently taking ibrutinib do not need to undergo a washout period o Limited palliative radiation is allowed if ≥ 2 weeks from C1D1 o Corticosteroid therapy (prednisone or equivalent ≤ 20 mg daily) is allowed as clinically warranted as long as the dose is stabilized at least for 7 days prior to initial dosing. Topical or inhaled corticosteroids are permitted. • Autologous hematologic stem cell transplant within 3 months of study entry. Allogeneic hematologic stem cell transplant within 12 months. Post-allo patients must not have active graft versus-host disease and be off all immune suppression (other than steroids, as above) • Evidence of active Hepatitis B (not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or active Hepatitis C infection. Evidence of active HIV infection. • Active central nervous system involvement by lymphoma • Requires treatment with strong CYP3A4/5 inhibitors (See Appendix J) • Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: o Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV [see Appendix H]) o QTcF >470 msec o Angina not well-controlled by medication o Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months • In the phase Ib portion of the study, CLL patients who have previously received ibrutinib will be ineligible o MCL patients who have been on ibrutinib for less than 6 months (180 days) from the time of registration are eligible in the Ib portion of the trial. No washout will be required. • Presence of other active cancers, or history of treatment for invasive cancer within the past 2 years. Patients with stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e. noninvasive) are eligible, as are patients with history of non-melanoma skin cancer and patients with localized prostate cancer on watch and wait. • Patients who require warfarin for anticoagulation (other anticoagulants are allowed) • Women who are pregnant or lactating
Study Duration	Approximately 18 months to accrue, plus follow-up

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1. OBJECTIVES

1.1 Study Design

This is a phase I/Ib study to evaluate the maximum tolerated dose, characterize safety, and obtain preliminary efficacy data of TGR-1202 in combination with ibrutinib in relapsed/refractory CLL and MCL.

1.2 Primary Objectives

- To determine the maximum tolerated dose (MTD) of TGR-1202 when used in combination with ibrutinib in patients with relapsed or refractory CLL or MCL.

- To evaluate the safety and determine any dose limiting toxicities (DLTs) of TGR-1202 in combination with ibrutinib in patients with relapsed or refractory CLL or MCL.

1.3 Secondary Objectives

- To preliminarily characterize the efficacy of TGR-1202 at its MTD in combination with ibrutinib by determining the overall response rate (ORR) defined as the sum of the complete response (CR) and partial response (PR) rate, as well as to determine the rate of nodal response with lymphocytosis (nPR), progression-free survival (PFS), and duration of response (DOR).

1.4 Exploratory Objectives

- To assess whether apoptotic priming as determined by BH3 profiling and pharmacodynamic response as determined by phospho-flow are predictive of clinical response.

2. BACKGROUND

2.1 Study Diseases

Chronic lymphocytic leukemia (CLL) affects mainly older adults and is the most common leukemia in the Western Hemisphere. In the US, an estimated 16,060 new cases of Chronic Lymphocytic Leukemia were reported in 2012, with deaths totaling 4,580 due to the disease according to National Cancer Institute (NCI) estimates (1). While CLL in general is responsive initially to current therapies, it remains an incurable disease, and there are several higher risk cytogenetic abnormalities which are particularly difficult to treat. Once such abnormality is deletion of a part of the short arm of chromosome 17 del(17p). Patients with del(17p) are usually resistant to conventional chemotherapies and have an overall survival on the order of 2-3 years, even with treatment. Thus, there is a pressing need for new, innovative, targeted therapies for the treatment of this heterogeneous group of diseases. Recently, ibrutinib was approved by the FDA for the treatment of relapsed or refractory CLL patients, including those with del 17p, after

displaying high activity in this high risk patient population, with nearly 90% of patients achieving at least a partial response or partial response with lymphocytosis, and a progression free survival of 75% at 26 months (2).

Mantle Cell Lymphoma (MCL) accounts for approximately 6% of all non-Hodgkin lymphoma (NHL), and is also more likely to affect males. The median age of diagnosis for MCL is in the mid-60s. MCL is particularly difficult to treat since it shares features of aggressive lymphomas often with relentless disease progression, yet more like indolent lymphomas is considered incurable with conventional therapies. Rituximab (Rituxan) is used widely, generally in combination with chemotherapy in the front line and second line settings. FDA-approved treatment options for patients with relapsed refractory MCL include the proteasome inhibitor bortezomib and the immunomodulatory agent lenalidomide both of which have modest response rates and limited durability of response. Recently, ibrutinib was also approved for the treatment of relapsed and refractory MCL, based on a response rate of 68%, including 21% CR, with an estimated median PFS of 13.9 months (3).

Despite the array of available therapies, both CLL and MCL remain incurable diseases, with many patients achieving no response at all, or attaining a less than optimal response to these therapies and often relapsing with recurrent disease. Moreover, despite the high level of activity of ibrutinib, few patients achieve complete remission with this agent, and without complete remission it is unlikely these patients will achieve cure. Therefore, there is a pressing need for new, innovative, combinations of targeted therapies for the treatment of these diseases.

2.2 **B cell receptor pathway (BCR)**

Over the last few years, it has been recognized that the B cell receptor (BCR) pathway is a promising, novel target for the treatment of CLL (Figure 1). Although not activated by somatic mutation, nonetheless the BCR pathway is constitutively active in CLL and further inducibly activated within microenvironmental niches. Upregulation of the B cell receptor (BCR) pathway is now thought to be a hallmark of the pathophysiology underlying chronic lymphocytic leukemia (CLL).

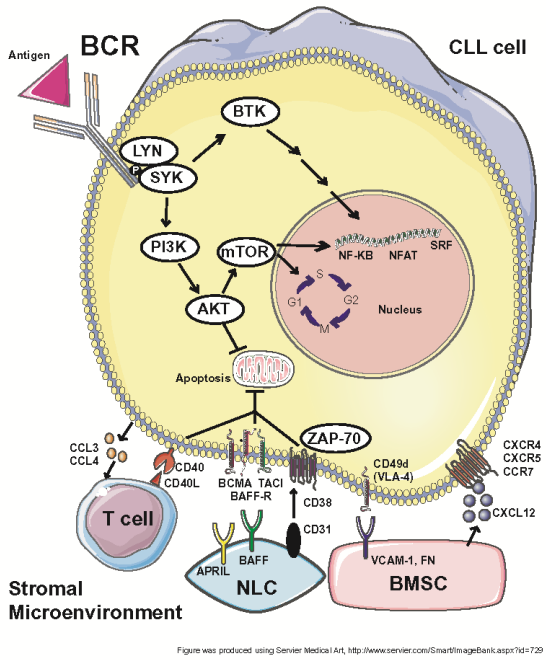


Figure 1. The B cell receptor (BCR) signaling pathway and molecular interactions in the CLL microenvironment (4)

2.3 Bruton's Tyrosine Kinase

A key protein in the BCR pathway is Bruton's tyrosine kinase (BTK). Loss of function mutations in BTK result in the human disease X-linked agammaglobulinemia (Bruton's agammaglobulinemia), which leads to profound gamma globulin deficiency and increased risk of infection. *In vitro* inhibition of BTK results in abrogation of survival signaling downstream of the BCR, a decrease in pro-survival cytokines, and modest induction of CLL cell apoptosis (5). Moreover, inhibition of BTK in CLL cells *in vitro* with siRNA promotes apoptosis, and BTK inhibition in the TCL1 mouse model of CLL significantly delays the development of CLL, suggesting that BTK is a critical kinase for CLL development and expansion (6).

2.4 Phosphatidylinositol 3-kinase (PI3K)

Phosphatidylinositol 3-kinase (PI3K) inhibitors can have a profound impact on modulating the CLL microenvironment (7). For example, the delta-isoform specific PI3K inhibitor idelalisib (GS1101) was found *in vitro* to inhibit microenvironmental protection by releasing CLL cells from stroma, thereby leading to increased CLL cell susceptibility to cell death (8). These promising preclinical results of PI3K inhibition in CLL have translated into the clinic, where a phase I trial of idelalisib showed that 72% of CLL patients achieved a lymph node response (9), and a recently published phase 3 randomized study of idelalisib plus rituximab vs. rituximab alone in relapsed/refractory CLL showed an 81% response rate, with a 12% absolute improvement in overall survival in the idelalisib arm compared to rituximab alone (5).

Though promising, PI3K-δ specific inhibition has potential limitations. For example, by

targeting only the δ-isoform of PI3K, CLL cells could theoretically develop resistance through upregulation of other PI3K isoforms. Therefore, it is logical to explore the use of a PI3K- δ inhibitor in combination with an inhibitor targeting a different protein in the BCR pathway such as BTK.

2.5 IND Agents

2.5.1 TGR-1202

TGR-1202 is a highly specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity for the delta over the alpha, beta, and gamma isoforms of PI3K. The PI3Ks are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated in various hematologic malignancies (7). TGR-1202 has demonstrated safety and preliminary efficacy in an ongoing Phase I clinical trial in patients with hematologic malignancies. TGR-1202 is manufactured by Alembic Pharmaceuticals and supplied by TG Therapeutics, Inc.

In the summer of 2017, TG Therapeutics announced that TGR-1202 will henceforth be referred to as umbralisib, though the name TGR-1202 will continue to be used for the purposes of this trial.

2.5.2 Pre-Clinical Evaluations of TGR-1202

In Vitro Activity

The potency of TGR-1202 against the human and mouse δ isoform of PI3K was evaluated in a homogeneous time resolved fluorescence (HTRF) based enzyme assay in the presence of ATP at its K_m value (100 μM) (10). Selectivity over the other three isoforms, namely, α, β, and γ was also determined (10, 11, 12, 13). Data demonstrated the specificity of TGR-1202 towards PI3Kδ with >1000, 50 and 48-fold selectivity over α, β, and γ, respectively in an enzyme based assay, indicating that the primary mode of action of this compound is via inhibition of the δ isoform.

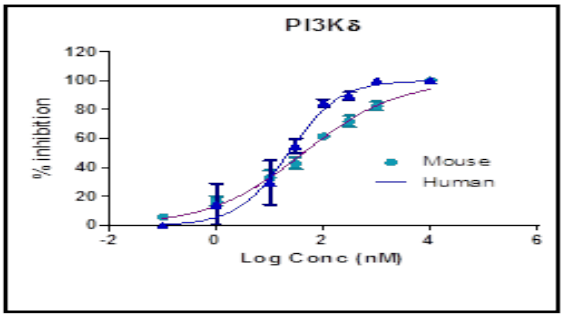


Figure 2. TGR-1202 potency against human and mouse PI3K isoforms

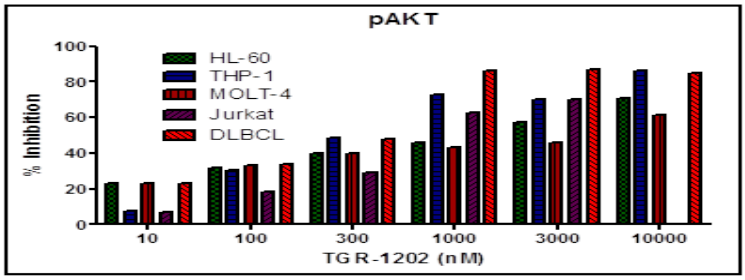
PI3K isoforms (Human)	IC_{50} (nM)
α	>10,000
β	1,116
γ	1,065
δ	22.23

Proliferation of immortalized leukemic cells representative of various indications was determined by a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay (14). Cells were incubated with TGR-1202 for different time-periods (72 -96 h) based on their

doubling time. Data demonstrated the ability of TGR-1202 to inhibit leukemic cell proliferation albeit with different potencies based on the cell type. Overall, a 50% growth inhibition for majority of B, T, and monocytic cell lines was achieved at a concentration between 0.5 -7.5 µM of TGR-1202 (Figure 2).

As a marker of pharmacodynamic engagement of target, the effect of TGR-1202 on AKT phosphorylation (15, 16, 17, 18, 19) was determined. AKT, a serine threonine kinase mediates the downstream effects of PI3K activity and modulates several cell processes including survival and growth. Reduction of phosphorylated AKT by TGR-1202 in representative cell lines was determined by Western blotting using a phospho-AKT (Ser473) antibody (Figure 3).

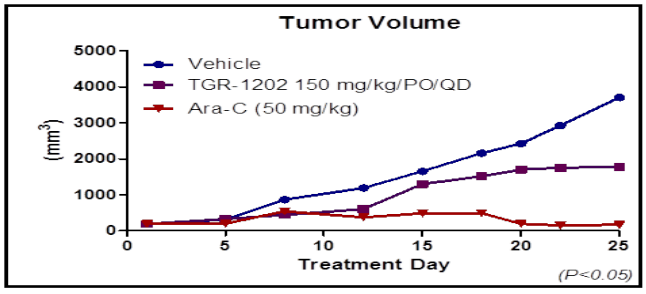
Figure 3. Reduction of pAKT by TGR-1202 in cell lines by Western blotting



2.5.3 *In Vivo* Activity

In vivo efficacy of TGR-1202 was confirmed in a subcutaneous mouse MOLT-4 xenograft model, representative of human T-cell acute lymphoblastic leukemia. Oral administration of 150 mg/kg/QD over a 25-day period resulted in a significant delay in tumor growth (Figure 4).

Figure 4. TGR-1202 *In vivo* efficacy



Toxicology

To assess the safety and toxicity of TGR-1202 a 28-day repeat dose study with a 14-day recovery period was conducted in CD-1 mice and beagle dogs, to evaluate the potential reversibility of findings and to support the use in humans. TGR-1202 was administered orally in order to mimic the planned mode of clinical administration.

Once daily oral administration of TGR-1202 was tolerated in mice at free base dose levels of 50 and 150 mg/kg/day. Increases in liver weights, microscopic findings in the liver and the increases in serum cholesterol, and female only ALT, AST, and GGT levels were observed at

750 mg/kg/day of free base (the highest dose tested) and were considered adverse. The no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg/day in mice.

Once daily oral administration by capsule of TGR-1202 was well tolerated in dogs at levels of 50 and 150 mg/kg/day. The gastrointestinal tract, based on clinical signs, was the target organ system. Based on effects on body weight and the incidence and severity of emesis and diarrhea, the NOAEL was considered to be 150 mg/kg/day (114.5 mg/kg/day as free base) in this species. Refer to the TGR-1202 Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

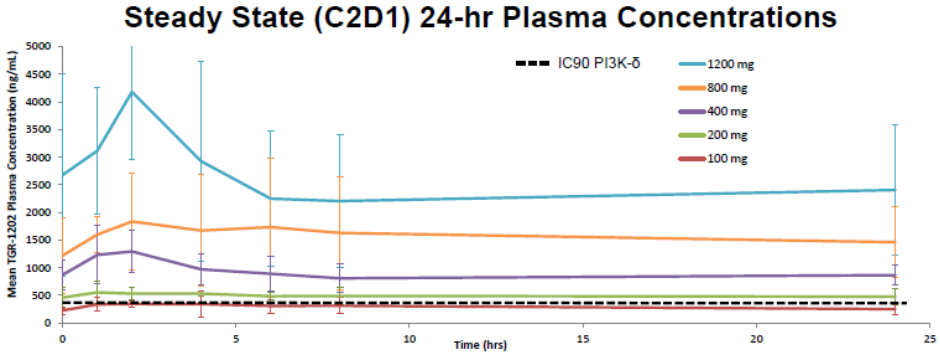
2.5.4 Clinical Development of TGR-1202

TGR-1202 is being evaluated in an ongoing single-agent Phase I dose-escalation study in patients with relapsed and refractory hematologic malignancies. As of June 1, 2014, 40 patients have been evaluated with single agent TGR-1202 at doses as high as 1800 mg QD.

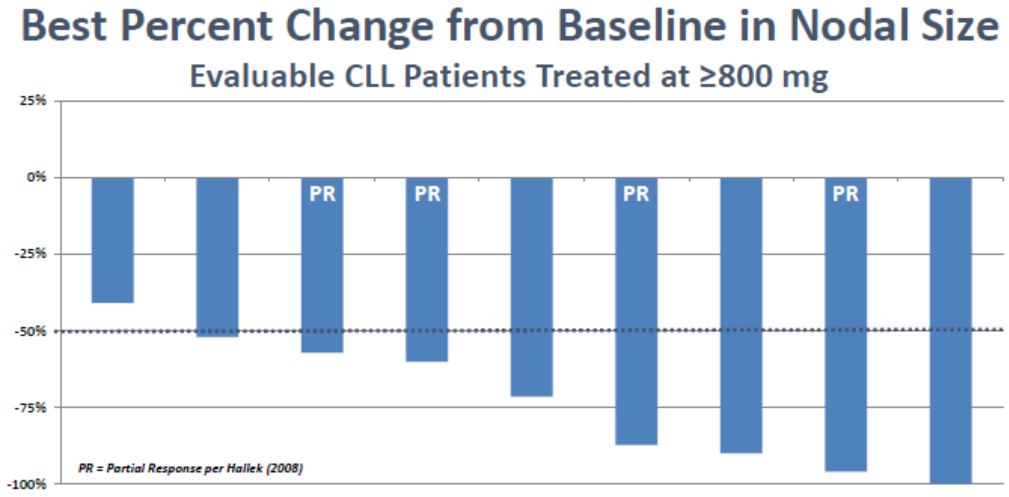
As of June 1, 2014, 21 of the 36 evaluable patients remained on TGR-1202 treatment. No safety concerns have been recognized or reported as documented by the Study Chair and Medical Monitor for the trial for up through 1200 mg QD (the highest dose that has cleared DLT evaluation). Preliminary data from this ongoing Phase I study was presented at the 2013 Annual Meeting of the American Society of Hematology (20) and updated at the 2014 European Hematology Association Annual Congress (21), as summarized below:

<u>Safety:</u>
One DLT event of Grade 3 rash was observed at the 800 mg dose level, which necessitated enrollment of an additional 3 patients. The Grade 3 rash resolved upon suspension of TGR-1202 and concomitant medications and did not recur upon re-challenging the patient at 800 mg QD. No other DLTs have been reported through 1200 mg QD dosing and adverse events have been manageable, with those occurring in greater than 5% of patients and deemed at least possibly related to TGR-1202 consisting of the following : diarrhea (18%), nausea (16%), vomiting (13%), fatigue (10%), neutropenia (8%), hypokalemia (8%), and weakness (8%).

<u>Pharmacokinetics:</u>
TGR-1202 was rapidly absorbed (mean T_{max} ~2 hours), and displayed a Cycle 1, Day 1 half-life of ~9 hours. Steady state pharmacokinetics were achieved by Day 15 of dosing, with an estimated steady state half-life of ~50 hours observed. Kinetics were observed to be linear through 1200 mg QD dosing.



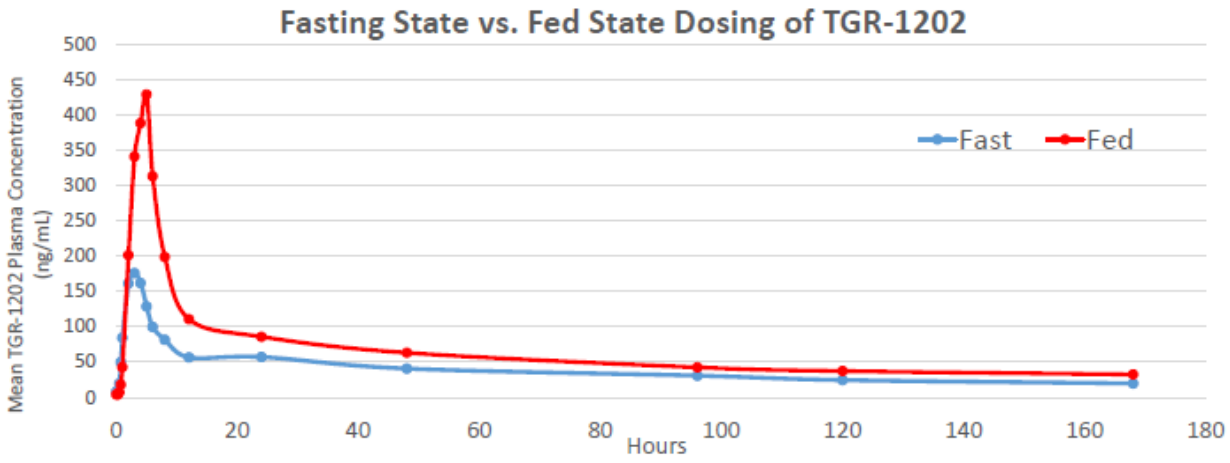
Efficacy:
A significant dose-response relationship was observed with patients treated at higher doses (400 mg QD or greater) demonstrating marked reduction in tumor burden. Of the 9 evaluable CLL patients treated at 800 mg QD or higher (including those that started at a lower dose and were escalated to 800 mg), 8 achieved a nodal response (>50% reduction in lymphadenopathy), while the ninth patient achieved a significant nodal reduction (>40%) at first scan. Of the 8 patients achieving a nodal response, 4 have achieved a partial response per IW-CLL (6) criteria.



Overall, TGR-1202 was well tolerated and displays promising signs of clinical activity.

Reformulation and Change to Fed State Dosing
The initial dosing in the Phase I single agent study for Cohorts 1 through 7 was conducted in a fasting state, with patients instructed to take TGR-1202 having fasted for 2 hours prior, and 1 hour post study drug administration. Given the formulation of TGR-1202 in 200 mg tablets, study drug administration at higher dose levels (i.e. 1200 mg QD or greater) resulted in an unfavorable number of tablets for daily administration, prompting the exploration of dosing alterations to improve absorption.

Food Effect
As TGR-1202 is a BCS Class 2 drug, a positive food-effect was hypothesized and tested in a 24-subject, pharmacokinetic crossover study assessing the relative bioavailability of a single dose of TGR-1202 administered in either a fasting state or following consumption of a standardized high-fat meal. Results indicated a positive food effect, with increased TGR-1202 exposure when dosing in a fed state, as detailed below.

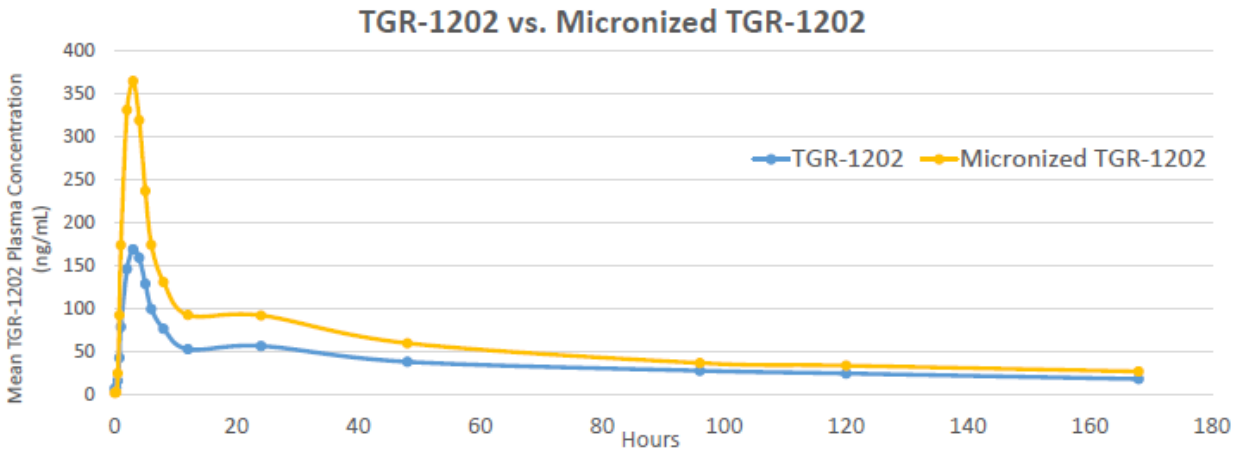


Parameters	Geometric LS Means		Ratio	90% C.I.
	Fasting State	Fed State		
AUC_{0-t} (ng·hr/mL)	6029.87	9692.02	1.61	1.40 – 1.84
AUC_{0-inf} (ng·h r/mL)	8391.35	14047.17	1.67	1.42 – 1.98
C_{max} (ng/mL)	176.78	483.15	2.73	2.34 – 3.19

Following analysis of this data, fed state dosing was implemented in select expansion cohorts which were opened at doses that had previously cleared DLT evaluation (800 mg and 1200 mg QD), both of which cleared DLT evaluation with no DLTs observed.

Micronized Formulation

In an effort to further improve the oral bioavailability of TGR-1202, the particle size of the drug product was reduced through a micronization process. A 24 subject pharmacokinetic bioequivalence/bioavailability (BE/BA) crossover study in healthy volunteers was undertaken to evaluate the relative oral bioavailability of TGR-1202 and micronized TGR-1202, with all patients dosed in a fasting state as a control. The results indicate markedly higher TGR-1202 exposure with micronized TGR-1202, as illustrated below:



Parameters	Geometric LS Means		Ratio	90% C.I.
	Current TGR-1202	Micronized TGR-1202		
AUC_{0-t} (ng·hr/mL)	5906.11	9439.82	1.60	1.49 – 1.71
AUC_{0-inf} (ng·h r/mL)	7715.67	12378.19	1.60	1.46 – 1.76
C_{max} (ng/mL)	166.20	371.70	2.24	2.02 – 2.47

A 2-fold increase in AUC is projected with micronized TGR-1202 compared to TGR-1202, and further 1-2-fold increase in AUC is projected with fed state dosing with a non-calorically standardized meal in uncontrolled conditions, which, when combined results in a projected 3-4-fold increase in TGR-1202 exposure with micronized TGR-1202 dosed in a fed state over the previous formulation of TGR-1202 in a fasting state.

2.6 Ibrutinib

Ibrutinib is a selective and potent covalent inhibitor of Bruton's Tyrosine Kinase (BTK), an enzyme found in the B-cell Receptor pathway which has been found to regulate B-cell proliferation and survival. Ibrutinib has demonstrated impressive single-agent activity in a number of B-cell malignancies including CLL/SLL and MCL. In a Phase Ib/II study of single agent ibrutinib in 85 patients with relapsed or refractory CLL/SLL, an overall response rate of 71% (89% including nodal response with lymphocytosis) was reported with manageable toxicity (2). Similarly, a 68% ORR was observed in a Phase II study of single agent ibrutinib in 111 patients with relapsed or refractory MCL (3). Ibrutinib is approved for the treatment of patients with relapsed or refractory MCL and CLL and is manufactured and supplied by Pharmacyclics, Inc. For more information on the safety and efficacy profile of ibrutinib, refer to the ibrutinib label available at www.accessdata.fda.gov.

2.7 Rationale

TGR-1202 is a highly specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ)

inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The delta isoform of PI3K is highly expressed in malignant lymphocytes, where it serves as a key node in the B cell receptor (BCR) signaling pathway, thereby making this an attractive target for selective inhibition of malignant B cells (4) TGR-1202 is currently in a Phase I dose escalation trial, evaluating sequentially higher single agent doses until a maximum tolerated dose (MTD) is determined.

Ibrutinib is an inhibitor of Bruton's Tyrosine Kinase (BTK), another key enzyme found at a different point in the BCR pathway, which has been found to be critical for B-cell proliferation and survival. Ibrutinib is approved for the treatment of patients with relapsed or refractory Mantle Cell Lymphoma (MCL) and Chronic Lymphocytic Leukemia (CLL). Although ibrutinib monotherapy is a promising therapy for relapsed CLL and MCL, not all patients respond to ibrutinib therapy, and in patients who do respond, it is inevitable that resistance mechanisms will arise, such as the C481S binding site mutations recently described in CLL (22). Notably, while 71% of CLL patients achieved an objective response to single agent ibrutinib, only 2% of patients achieved a CR, with the remainder of patients achieving a PR. Additionally, patients with high risk cytogenetics (deletion 17p) displayed a shorter progression free survival compared to those patients with normal cytogenetics (2). Similarly, the majority of responses seen with ibrutinib in patients with relapsed or refractory MCL were PRs (CR rate of 21% compared to PR rate of 47%), with a median PFS observed to be 13.9 months, indicating room for improvement (23).

Dual inhibition of both PI3K-delta and BTK may result in more complete BCR pathway blockade, and has the potential to overcome resistance mechanisms that may arise with targeting only one protein in this pathway. Dual BCR pathway blockade therefore has the potential to drive deeper responses for longer durations and also the reduced likelihood of developing treatment resistance.

The purpose of this study is to determine the MTD of the PI3K-delta inhibitor TGR-1202 in combination with the BTK inhibitor ibrutinib, and to explore the safety and efficacy of these two novel, oral, once daily, targeted agents in patients with relapsed refractory CLL and MCL.

2.8 **Correlative Studies Background**

2.8.1 BH3 Profiling

This study will incorporate a laboratory technique known as BH3 profiling, which is a functional assay we previously developed that detects the proximity of malignant cells to the threshold of apoptosis (what we call 'priming') through physiologic interrogation of BCL-2 family members. To perform a BH3 profile, we add individual BH3-only peptides to gently permeabilized primary CLL cells and use FACS to determine the amount of mitochondrial depolarization induced by each peptide, as measured by cytochrome c release.

We previously showed using primary CLL samples co-cultured with stroma *in vitro* that BCR inhibition can release CLL cells from stroma, and thereby increase priming for apoptosis (23). We also found that in a small, heterogeneously treated cohort of CLL patients, increased priming

was associated with improved clinical response. Building on these initial studies, we will incorporate BH3 profiling into this clinical trial to determine whether priming predicts degree of clinical response in this homogeneously treated patient population.

We hypothesize that patients whose cells undergo significant depolarization to BIM BH3 peptide (highly primed) will have superior clinical response to TGR-1202 and ibrutinib compared to patients whose cells undergo minimal BIM BH3 depolarization (unprimed). These assessments will be made on circulating CLL cells from the peripheral blood drawn from patients at baseline and correlated with our efficacy endpoints. If we have positive bone marrow aspirates available, we will also perform BH3 profiling to see whether the level of priming in CLL cells from the marrow is a better predictor of response than the level of priming in peripheral blood CLL cells.

2.8.2 Pharmacodynamic Markers

Where possible, pharmacodynamic markers may be assessed to determine how effectively ibrutinib plus TGR-1202 are hitting their proposed targets *in vivo*. Using pretreatment and week 1 patient samples, we will use phosphoflow cytometry to determine the levels of phospho-AKT, phospho-BTK, and phospho-ERK compared to total AKT, BTK, and ERK, respectively. These analyses may be confirmed in a subset of patients by Western Blot. In addition, recent work has suggested that reduction in the cell proliferation marker Ki-67 in peripheral blood CLL cells occurs rapidly in patients treated with BCR pathway antagonists, and we may assess this also by phosphoflow cytometry.

2.8.3 Genomic Markers

In addition, saliva as a source of germline will be collected prior to study initiation and may be collected more than once if inadequate specimen is obtained. All samples will promptly be delivered to the laboratory of Dr. Jennifer Brown, where DNA will be extracted and then sent to the Broad Institute (Cambridge, MA) for whole exome sequencing.

2.8.4 Genzyme Minimal Residual Disease

Blood and Bone marrow samples will be collected to confirm complete response for minimal residual disease analysis by Genzyme Genetics (LabCorp Specialty Testing Group/Integrated Oncology) by flow cytometry. Preliminary molecular analysis will be done at baseline on peripheral blood.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Confirmed diagnosis of Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL), or Small Lymphocytic Lymphoma (SLL)

3.1.1.1 MCL patients must have:

- At least 1 measurable site of disease according to Revised Response

Criteria for Malignant Lymphoma
- Received at least 1 prior standard therapy for MCL

3.1.1.2 CLL/SLL patients must have:
- Indication for treatment according to the 2008 IWCLL Criteria (5)
- Received at least one prior standard treatment regimen

3.1.2 Patients must be at least 18 years of age

3.1.3 ECOG performance status ≤2 (Appendix G)

3.1.4 Participants must have normal organ and marrow function as defined below:
- Absolute neutrophil count (ANC) ≥ 500 independent of growth factor support and platelet count ≥ 30,000 independent of transfusion support. (*Patients who have cytopenias due to significant bone marrow infiltration do not have to meet hematologic eligibility criteria. Significant bone marrow infiltration is defined as >50% involvement by CLL.)*

- Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) unless due to Gilbert's disease or hemolysis, then ≤ 3.0 times ULN

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.0 x ULN if no liver involvement or ≤ 4 x the ULN if known liver involvement

- Creatinine ≤2.5 mg/dL OR calculated creatinine clearance ≥50 mL/min (as calculated by the Cockcroft-Gault method)

3.1.5 Ability to swallow and retain oral medication

3.1.6 Female patients who are not of child-bearing potential (see Appendix C), and female patients of child-bearing potential who have a negative serum pregnancy test at study screening. A tubal ligation is sufficient documentation that a patient is not of child bearing potential. Female patients of child-bearing potential (see Appendix C), and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 30 days after the last dose of either study drug.

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

3.2 Exclusion Criteria

3.2.1 Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) within 3 weeks of Cycle 1/Day 1 with the following exceptions:

- Limited palliative radiation is allowed if completed ≥2 weeks of C1D1
- Corticosteroid therapy (prednisone or equivalent ≤20 mg daily) is allowed as clinically warranted as long as the dose is stabilized at least for 7 days prior to initial dosing. Topical or inhaled corticosteroids are permitted
- Patients currently taking ibrutinib do not need to undergo a washout period

3.2.2 Autologous hematologic stem cell transplant within 3 months of study entry. Allogeneic hematologic stem cell transplant within 12 months. Post allo patients must not have active graft versus-host disease and be off all immune suppression (other than steroids, as above).

3.2.3 Participants who are receiving any other investigational agents.
- Patients who have previously received ibrutinib will be ineligible in the Phase Ib portion of the study of the CLL arm
- MCL patients who have been on ibrutinib for less than 6 months (180 days) from the time of registration are eligible in the Ib portion of the trial. No washout will be required.

3.2.4 Evidence of active Hepatitis B (not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or active Hepatitis C infection. Evidence of active HIV infection.

3.2.5 Active central nervous system involvement by lymphoma

3.2.6 Requires treatment with strong CYP3A4/5 inhibitors (See Appendix J)

3.2.7 Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
- Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV [see Appendix H])
- QTcF >470 msec
- Angina not well-controlled by medication
- Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months

3.2.8 Presence of other active cancers, or history of treatment for invasive cancer within the past 2 years. Patients with stage I cancer who have received definitive local treatment, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e. noninvasive) are eligible, as are patients with history of non-melanoma skin cancer and patients with localized prostate cancer on watch and wait.

3.2.9 Women who are pregnant or are lactating

3.2.10 Patients who require warfarin for anticoagulation (other anticoagulants are allowed)

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

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

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

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

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

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Research Project Manager. All sites should call the Research Project Manager at 617-632-6325 to verify dose level availabilities.

Following registration, participants should begin protocol therapy as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and faxed to 617-632-5152 or e-mailed to the Research Project Manager:

- Documentation of diagnosis, prior therapy, baseline assessments and any other documentation relevant to the inclusion/exclusion criteria (see section 3 for details)
- Signed participant consent form
- HIPAA authorization form (if appropriate)
- DF/HCC Eligibility checklist (provided by the lead site)

The participating site will then call or e-mail/ the lead site to verify eligibility. The research project manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The research project manager will fax or e-mail the participant study number, and the dose treatment level, to the participating site. The Study Coordinator will also contact the participating site and verbally confirm registration

NOTE: Registration with the Office of Data Quality can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

5.1 Pre-treatment Criteria

5.1.1 Cycle 1, Day 1

Participants must have met all of the inclusion criteria and have none of the exclusion criteria at screening. Participants must be registered to the protocol prior to initiating therapy.

5.1.2 Subsequent Cycles

Patients can receive treatment if they do not meet dose delay/dose modification criteria (see section 6). All toxicities must have resolved to grade 1 or less, or the patient's baseline, prior to initiating subsequent cycles.

5.2 Treatment Regimen Phase 1

Cycle = 28 days

Dose Level	TGR-1202 Dose	Ibrutinib Dose MCL	Ibrutinib Dose

			CLL
1	400 mg	560 mg	420 mg
2	600 mg	560 mg	420 mg
3	800 mg	560 mg	420 mg
If ≥ 2 DLT's in either Cohort 1, 3- 6 pts will enroll in Cohort -1 as follows:			
-1	200 mg	560 mg	420 mg
If ≥ 2 DLT's in a Cohort –1 treatment group, study will be terminated			

Dose level 1 will be the starting level for patients in both the CLL and MCL arms. Patients will continue daily administration of TGR-1202 + ibrutinib until progression or removal from study per investigator decision.

5.2.1 Tumors lysis syndrome (TLS) prophylaxis

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

5.2.2 Cohort Review

The sponsor representative and Principal Investigator will be in charge of reviewing safety data (SAE's / AE's) after the 3rd patient of Cohort 1 (or Cohort 2 and Cohort 3), per MCL and CLL group, is treated on Day 28 of Cycle 1. They will recommend whether or not it is possible to continue to Cohort 2 and 3 or if currently in Cohort 3, move into the Phase Ib portion of the study for each MCL and CLL group independently as per the study design. This decision will be made after a teleconference with the other investigators to obtain their input.

CLL/SLL

Agent	***Dose***	***Route***	***Schedule***	***Cycle Length***
TGR-1202	Cohort 1: 400 mg Cohort 2: 600 mg Cohort 3: 800 mg	PO in the a.m. with food.*	Days 1-28, continuous	28 days (4 weeks)
Ibrutinib	420 mg	PO in the p.m.	Days 1-28, continuous	

* Patients should be instructed to take TGR-1202 with food, preferably within 30 minutes of a meal.

MCL

Agent	***Dose***	***Route***	***Schedule***	***Cycle Length***
TGR-1202	Cohort 1: 400 mg Cohort 2: 600 mg Cohort 3: 800 mg	PO in the a.m. with food.*	Days 1-28, continuous	28 days (4 weeks)
Ibrutinib	560 mg	PO in the p.m.	Days 1-28, continuous	

* Patients should be instructed to take TGR-1202 with food, preferably within 30 minutes of a meal

The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle. See Appendices E and F, MCL and CLL respectively, for diary.

5.2.3 Phase I Dose Confirmation

The safety of TGR-1202 in combination with ibrutinib will be assessed using a standard 3 + 3 dose-escalation design, with a starting dose of TGR-1202 at 400 mg (Cohort 1) followed by 600 mg (Cohort 2), followed by 800 mg (Cohort 3) and the possibility of a single dose escalation or de-escalation based on safety in the first 3-6 patients in a given cohort. The DLT observation period is the first cycle (28 days). The ibrutinib dose will be fixed at the FDA-approved doses of 420 mg (CLL) or 560 mg (MCL).

A cohort of 3 patients will enter at each dose level. If no DLT is seen in the first 3 eligible patients at any dose level, then a dose escalation will take place.

If 2 or more of the 3 eligible patients experience DLT at dose level 1 (400mg), dose level 2 (600 mg), or dose level 3 (800 mg), the next cohort of 3 patients will be treated at the next lower dose level, unless 6 patients have already been treated at that dose level. If 2 or more of the 3 eligible patients experience DLT at dose level -1 (200 mg), the study will be terminated early.

If 1 of the first 3 patients experiences DLT then 3 additional patients will be treated at that dose level. If there is no DLT in the 3 additional patients then dose escalation will take place. If this is does level 3 or -1, this dose is the MTD. If 1 or more of the 3 additional patients experience(s) DLT then the MTD is considered exceeded, and 3 more patients are treated at the next lower dose, unless 6 patients have already been treated at that dose level. If this is dose level -1, the study will be terminated early.

A minimum of six patients must be evaluated at the highest tolerated dose level prior to proceeding to Phase Ib, and fewer than 2 patients in 6 should experience DLT.

# DLT	Dose Escalation
0/3	Accrue 3 new patients at next higher dose level. (if this is dose level 3 or -1, accrue additional 3 patients at this dose level)
1/3	Accrue additional 3 patients at current dose level
1/3 + 0/3	Accrue 3 new patients at next higher dose level (if this is dose level 3 or -1, this is the MTD)
1/3 + ≥ 1/3	Previous dose level is MTD if 6 treated at that level (if this is dose level -1, terminate the study)
≥ 2/3	1) Prior dose level is MTD (if 6 treated at that level) 2) De-escalate dose, accrue additional 3 patients at prior lower level (if only 3 treated at the level thus far) 3) If this is dose level -1, terminate the study

Of note, the MCL and CLL arms of the study will be considered independently in terms of dose

escalation evaluation. However, should unexpected, emergent toxicity emerge in one of the arms, the impact of this event will be considered for both arms.

5.2.4 Stopping Rules for Phase I Dose-Escalation

The Principal Investigator will be in charge of reviewing safety data following the final treatment dose (Day 28 of Cycle 1) of the last patient in Cohort 1, Cohort 2 and Cohort 3, and will decide whether or not it is possible to proceed to the next scheduled cohort or Phase Ib portion of the trial. Principal Investigator will consult with a representative from TG Therapeutics before deciding on escalation. In order to ensure safety and limit toxicity for enrolled patients, dose modifications will be performed according to the schema described in Section 6.2. These events will be reviewed by the sponsor representative and Principal Investigator and potentially other study Investigators at the end of Cycle 1 and routinely thereafter during the course of the study. All other serious and non-serious adverse events will be documented, managed including possible reductions in dose according to investigator discretion, followed until resolution or stabilization, and will also be reviewed by the sponsor representative and Principal Investigator routinely during the course of the study.

5.3 Treatment Regimen Phase Ib

Once the MTD of TGR-1202 in combination with ibrutinib has been determined for either the MCL or CLL patient groups, independently, the Phase Ib part of the study will open. Subjects will be treated per the same dosing schedule as in the Phase I, as follows:

Treatment Schema for Phase Ib

Drug	
TGR-1202 (PO)	Daily Dosing – Days 1 – 28
Ibrutinib (PO)	Daily Dosing – Days 1 – 28

5.4 Treatment Assessments

Study calendar can be found in section 10.

5.4.1 Screening (within 21 days of C1D1)

- Informed consent
- Medical history, physical exam, vital signs (pulse, BP, temperature), PS
- Serum chemistry, hematology (within 21 days of C1D1)
- PT/PTT/INR
- Beta 2 microglobulin
- Serum Protein Electrophoresis (SPEP)
- Urinalysis (Macroscopic only)
- HBV, HCV, HIV assessment: HBV surface antigen, HBV surface antibody, HBV core antibody: if HBV core antibody is positive, must have a negative HBV viral load to enroll. HCV antibody: if positive, must have negative HCV viral load to enroll. HIV 1/2 antibody: must have negative result to enroll)
- Correlative study sample collection

- Serum Pregnancy (+/- 3 days C1D1)
- BM aspirate/biopsy (within 90 days prior to C1D1;Core, aspirate ,flow cytometry, cytogenetics and FISH at baseline if possible; Core, aspirate and flow cytometry for all marrows thereafter or at investigators discretion)
- EKG
- CT scan of the chest, abdomen, pelvis (and neck if palpable cervical adenopathy is present) within 30 days of C1D1
- FISH analysis (done locally per site standard)
    - MCL patients whose cytogenetics show 11;14 translocation do not require FISH analysis
- IGHV/TP53 and Zap70 status (CLL/SLL patients only unless already tested and enrolled on DFCI trial i.e.: 99-224-Performed through Integrated Oncology)
    - Patients who have had prognostic assessments (TP53, FISH or Zap70) performed within 6 months (at the center where they are being treated prior to registration) do not need to have these assessments repeated. IGHV does not need to be repeated if ever tested previously by Integrated Oncology (prior testing from other laboratories only with permission from overall PI)

5.4.2 Cycle 1, Day 1 (+/- 3 day window)

Participants must meet all of the inclusion criteria, have none of the exclusion criteria, and must be registered to the protocol prior to initiating therapy. See section 4 for more details on registration procedure. The laboratory tests at screening will be used to determine eligibility for this study. If laboratory tests need to be repeated for clinical reasons on C1D1, these values do not need to meet eligibility criteria again in order for the patient to start on treatment.

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology
- Correlative study sample collection

5.4.3 Cycle 1, Day 8 (+/- 3 day window)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology
- Correlative study sample collection

5.4.4 Cycle 1, Day 15 (+/- 3 day window)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology

5.4.5 Cycle 1, Day 22(+/- 3 day window)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication

- Serum chemistry, hematology

5.4.6 Cycle 2, Day 1 (+/- 3 day window)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology, PT/PTT/INR

5.4.7 Cycle 2, Day 15 (+/- 3 day window)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology

5.4.8 Cycle 3-6, Day 1 (+/- 3 day window)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology
- IgA, IgM, IgG (Only C3 Day1 and C6 Day 1 if no M- Protein detected at baseline)
- SPEP (Only C3 and C6 Day 1 only if M protein is detected at baseline)

5.4.9 Cycle 8-12 (every 56 days +/- 3 days)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology
- IgA, IgM, IgG if no M-Protein detected at baseline
- SPEP only if M-protein detected at baseline
- Correlative samples to be collected every 6 cycles after C1D1
- After Cycle 15 restaging, scans are required every 6 cycles (+/- 14 days) or more frequently until Cycle 36

5.4.10 Cycles 12-36 (every 84 days +/-7 days) **OR** Cycle 12-Onward (every 84 days +/-7 days) for those not being followed by a local hematologist/oncologist

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology
- SPEP only if M protein detected at baseline (every 6 cycles)
- IgA, IgM, IgG if no M-Protein detected at baseline (every 6 cycles)
- Correlative sample collection every 6 cycles after C1D1
- Bone marrow biopsy/aspirate and scans at investigator's discretion after Cycle 36

5.4.11 After the cycle 36 visit, patients will have the option of being seen every other visit (approximately every 6 cycles or 168 +/- 14 days) by a hematologist/oncologist locally instead of q3 month visits at the main research institution to reduce travel burden. For patients who elect to do this, the following will should occur at their local provider's office:

- Standard of care comprehensive blood count with differential and a comprehensive chemistry panel should be completed
- Adverse Event assessment will be done over the phone or by email between the patient and the main research nurse/investigator and documented in the EMR/study chart.
- For the visits that occur at the main research institution, assessments described in 5.4.10 will apply

5.4.12 Confirmation of Complete Response

- Bone Marrow Biopsy and Aspirate (Only in patients who had positive marrow at baseline to confirm CR)
- Correlative study sample collection

5.4.13 End of Treatment and or Disease Progression (next visit following a cycle after study drug was administered)

- Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
- Serum chemistry, hematology
- Correlative study sample collection
- BM biopsy/aspirate (only in patients who had a positive BM prior to study initiation and if considered SOC)

5.4.14 Follow-up

Patient visits should occur every 3 months and efficacy assessments should occur at investigator's discretion. For patients no longer treated at the original institution, phone contact should occur every 3 months with documentation of disease status or date of death obtained whenever possible. For those removed from treatment, survival follow up should occur every 3 months for up to 2 years, or until next CLL/MCL-directed therapy or death.

For patients evaluable for hematologic toxicity as per Appendix D, the ANC must be ≥ 500 and the platelet count must be ≥ 30K.

All non-hematologic toxicities except for alopecia must have resolved to ≤ Grade 2, or to the patient's baseline condition.

5.5 **Laboratory Assessments**

5.5.1 Hematologic

- CBC w/ differential, hemoglobin, hematocrit, platelets

5.5.2 Serum Chemistry

- Calcium, Sodium, Potassium, Phosphorus, Chloride, Glucose, Magnesium, Albumin, AST, ALT, Creatinine, BUN, Bicarbonate, Total protein, Total bilirubin (and direct bilirubin if total Bilirubin is abnormal), Uric acid, LDH, Alkaline phosphatase, lipase (only required at baseline)

5.6 **Agent Administration**

TGR-1202 and ibrutinib will be administered orally, both on an outpatient basis. There is no need for pre-treatment medications.

5.6.1 TGR-1202

TGR-1202 will be administered orally once daily. TGR-1202 will be self-administered (by the patient). Tablets should be taken at approximately the same time each day, preferably in the morning. Patients should be instructed to swallow the tablets as a whole and should not chew or crush them. **Patients should be instructed to take TGR-1202 with food and a full glass of water, preferably within 30 minutes of a meal. Patients should be instructed to take the dose of TGR-1202 in the morning.**

If a dose of TGR-1202 is missed, it should be taken as soon as possible on the same day. If it is missed for more than 4 hours, 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. All attempts should be made by the patient to return any extra drug in its original container and drug diaries to the study staff to confirm drug accountability.

No routine prophylactic antiemetics or premedications should be given outside of protocol requirements. However, these medications may be administered for symptoms when they occur, and may be given prophylactically afterwards

5.6.2 Ibrutinib

Ibrutinib will be administered orally once daily, preferably in the evening. Ibrutinib will be self-administered (by the patient). Capsules should be taken at approximately the same time each day. Patients should be instructed to swallow the capsules as a whole and should not chew or crush them. **Patients should be instructed to take the dose of the ibrutinib in the evening. Ibrutinib may be taken in either the fed or fasting state.**

If a dose of ibrutinib is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

No routine prophylactic antiemetics or premedications should be given outside of protocol requirements. However, these medications may be administered for symptoms when they occur,

and may be given prophylactically afterwards.

5.6.3 Dose-Limiting Toxicity- Cycle 1 for Phase 1 Only

Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) with the exceptions recommended by the IWCLL guidelines for the diagnosis and treatment of CLL defined in Appendix D.

Toxicity will be considered dose-limiting if it occurs during the first cycle (28 days) of treatment with TGR-1202 and ibrutinib, and is considered at least possibly related to either TGR-1202 and/or ibrutinib. Any event defined below, unless the investigator considers the event clearly unrelated to study drug or due to extraneous causes, will be considered a dose-limiting toxicity.

Dose-limiting toxicities will be defined as the following:

- Grade 4 anemia; Grade 4 neutropenia lasting >7 days (while receiving growth factor support); Grade 4 thrombocytopenia lasting > 7 days; Grade ≥3 febrile neutropenia; and Grade ≥3 thrombocytopenia with Grade >2 hemorrhage;
    - For patients with CLL/SLL, hematologic toxicity will be graded according to the IWCLL guidelines (Appendix D) and Grade 4 toxicity lasting >7 days will be considered dose limiting; this will not apply to CLL/SLL patients who are not evaluable for hematologic toxicity by IWCLL criteria (see Appendix D)
- Grade ≥ 3 non-hematologic toxicity unresponsive to standard supportive care measure with the exception of:
    - Asymptomatic Grade ≥3 lab abnormalities that resolve to ≤ Grade 1 or baseline within 7 days;
- Treatment delay of ≥14 days due to unresolved toxicity; and
- Non-hematologic toxicity of Grade 2 (at any time during treatment) that, in the judgment of the Investigators, Study Chair, and the Medical Monitor, is dose-limiting.

Adverse events meeting the above definitions but are clearly unrelated to study drug will not be considered DLTs. In rare instances an event may fall within the definition of a DLT as defined above but the event may not be considered a DLT (i.e., not clinically meaningful/significant). If this occurs, a discussion between the Principal Investigator, Investigator(s), a TG Therapeutics representative, will take place to thoroughly review the event and supporting data, and the reasons for not considering the event a DLT will be clearly documented with supporting rationale. In addition, other events may occur which do not meet the definition of a DLT but are concerning to the Principal Investigator, other Investigator(s) and/or the TG Therapeutics representative, and may be then considered to be DLTs.

5.6.4 Determination of Dosing-Limiting Toxicity- Cycle 1

The patient population used for determination of DLT will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. Minimum safety requirements will be met if, during Cycle 1 of treatment in the Phase I part of the study, the patient receives at least 80% of planned ibrutinib and TGR-1202 doses, completes the required safety evaluations, and is observed for at least 28 days following the first dose of TGR-1202 and ibrutinib. Patients who experience a DLT will be considered evaluable regardless of the number of doses received.

5.6.5 Replacement of Patients

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol. If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for inclusion in the DLT-determining population described above, that patient will be replaced.

5.7 General Concomitant Medication and Supportive Care Guidelines

The following treatments are prohibited while on clinical trial: other investigational drug treatments or study participation, radiation therapy (except as described above), hormonal therapy for cancer, cancer immunotherapy or other biologic therapy. Low dose glucocorticoids ($\leq$ 20 mg per day of prednisone or equivalent) may be administered for premedication or AE management after discussion with the Principal Investigator.

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

Antiemetics: Both TGR-1202 and ibrutinib are considered to be of low emetogenic potential, and therefore no anti-emetics are required by protocol, but may be used as needed at the investigators' discretion.

Tumor Lysis Syndrome: In subjects at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or institutional standards should be considered.

5.8 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. If a participant is found by the treating investigator and by the overall PI to show clinical benefit from study treatment, the patient may remain on treatment. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

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

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Patient requests to withdraw consent or discontinue treatment
- Pregnancy
- Inability of the patient to comply with trial requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Inter-current illness (this will be at the investigator's discretion)
- Non-compliance/lost to follow-up
- Discontinuation of the study by the Sponsor

After withdrawal from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of either trial drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the Case Report Form (CRF).

All patients who have CTCAE grade 3 or 4 laboratory abnormalities at the time of withdrawal should be followed until the laboratory values have returned to grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff. External sites should submit the form to the Research Project Manager.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Matthew Davids, MD at 617-632-6331, or page through 617-632-3352.

5.8.1 Pregnancy

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

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

If an investigator suspects that a patient may be pregnant after the patient has been receiving trial drug(s), the trial drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the trial drug(s) must be immediately and permanently stopped, the patient must be discontinued from the trial, and the investigator must notify the Overall PI as soon as possible. If a patient becomes pregnant while enrolled in the trial, an SAE

form should be completed and faxed to the Overall PI expeditiously. For more details regarding handling and reporting of pregnancies that occur during treatment, see Appendix C.

5.9 Duration of Follow Up

Participants will be followed for survival after discontinuing protocol therapy every 3 months for up to 2 years or until the patient receives their next CLL/MCL-directed therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

For patients continuing to follow up at the treating institution, regular visits should occur every 3 months and efficacy assessments should occur at the investigator's discretion. For patients no longer treated at the original institution, phone contact should occur every 3 months with documentation of disease status or date of death obtained whenever possible. Patients should be followed for survival every three months for up to two years or until death, or next CLL/MCL directed therapy.

5.10 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff. External sites should submit the form to the Research Project Manager.

6. DOSING DELAYS/DOSE MODIFICATIONS

Patients should be assessed clinically for toxicity at each visit using the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) grading scale. Hematologic toxicity for CLL patients will be assessed by the IWCLL defined in Appendix D.

Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

It should be noted that both TGR-1202 and ibrutinib are generally well-tolerated oral agents with favorable adverse event profiles. Therefore, where possible, investigators will be encouraged to

continue patients on the full dose of both drugs. The dose reduction criteria on this study are intentionally lenient to allow investigators to continue patients on full dose given the likelihood that many adverse events will be related to underlying disease and co-morbidities.

Dose modification and or intervention with supportive care recommendations for TGR-1202 (for ibrutinib follow prescribing information) are provided below, however, final discretion lies with the treating investigator in regard to more or less aggressive intervention. Decisions about which specific investigational agent (or if both agents) needs to be reduced, and actual dose reductions, as well as the number of dose reductions will be made after discussion between the treating investigator and the Principal Investigator

6.1 Critical Modifications

For CLL/SLL patients, the hematologic dose modifications are per the IWCLL Grading Scale (see Appendix D – Grading Scale for hematologic toxicity in CLL studies). All other dose modifications are graded by the CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE).

Note: If cytopenias are deemed related to the underlying disease rather than either TGR-1202 or ibrutinib, dose reductions are not required and are per investigator discretion.

Patients who experience an adverse event will be allowed to delay TGR-1202 and/or ibrutinib dosing by up to one month in order to recover from the toxicity. Patients may resume TGR-1202 and/or ibrutinib, provided that the toxicity has resolved to Grade ≤2 or baseline.

6.2 Dose Modifications of TGR-1202

If toxicity, in the opinion of the investigator, is at least possibly attributable to TGR-1202, the following guidelines for hematologic and non-hematologic toxicities should be followed in patients who are evaluable for hematologic toxicity:

Patients may remain on ibrutinib therapy alone if TGR-1202 has been discontinued, after discussion with the Overall PI.

6.2.1 Hematologic Toxicity

Table 1 Dose Modifications for Hematologic Toxicity (*For patients with CLL, Appendix D IWCLL Grading Scale should be referenced*).

Worst CTCAE Grade Toxicity	Recommended Action to be Taken
HEMATOLOGIC	
Neutropenia (ANC)	
Grade 1	Maintain dose level
Grade 2	**First incidence:** Maintain dose level **Second incidence:** Consider growth factor support

Grade 3 / 4 **1st Occurrence**	Hold dose until resolved to ≤ Grade 2 or baseline, consider growth factor support.
Grade 3 / 4 **Subsequent Occurrences**	Hold dose until resolved to ≤ Grade 2 or baseline, consider growth factor support. Consider reducing dose as per Table 3 if warranted.
Thrombocytopenia	
Grades 1,2, and 3 with no evidence of bleeding	Maintain dose level
Grade ≥3 thrombocytopenia with Grade >2 bleeding	Hold dose until to ≤ Grade 2 or baseline and bleeding resolves, consider platelet transfusion as necessary.
Grade 4 **1st Occurrence**	Hold dose until to ≤ Grade 2 or baseline, consider platelet transfusion as necessary.
Grade 4 **Subsequent Occurrences**	Hold dose until to ≤ Grade 2 or baseline, consider platelet transfusion as necessary. Consider reducing dose as per Table 3 if warranted.

6.2.2 Non-Hematologic Toxicities

Table 2 Dose Modifications for Non-Hematologic Toxicity

NON-HEMATOLOGIC	Recommended Action to be Taken
Grade 1 or 2	None
Grade 3 CTCAE	Hold dose until toxicity Grade ≤2 or baseline
If toxicity remains grade 3 toxicity for longer than 2 weeks	Consider reducing dose as per Table 3 if warranted or discontinue treatment
If grade 3 toxicity lasts 2 weeks and resolves to ≤ Grade 2	Hold dose until toxicity Grade ≤ 2 or baseline
Recurrence of Grade 3 toxicity	Consider reducing dose as per Table 3 if warranted
Grade 4 CTCAE	Hold dose until toxicity resolves to Grade ≤2 or baseline
Recurrence of Grade 4 toxicity	Consider reducing dose as per Table 3 if warranted or discontinue study drug

6.2.3 Dose Modification Guidelines

Table 3 Dose Modification Guidelines

Dose Level	Current TGR-1202 Dose	Modified TGR-1202 Dose (first dose reduction)	Modified TGR-1202 Dose (second dose reduction)
1	400 mg	200 mg	Discontinue study drug
2	600 mg	400 mg	200 mg
3	800 mg	600 mg	400 mg
-1	200 mg	Discontinue study drug	N/A

6.3 Dose Modifications of Ibrutinib

If toxicity, in the opinion of the investigator is attributable to ibrutinib, the investigator and research team should follow recommendations per ibrutinib's FDA approved prescribing information and/or per investigator discretion.

Ibrutinib should be held at least 3 to7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Patients may remain on TGR-1202 therapy alone if ibrutinib has been discontinued, after discussion with the Overall PI.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following list of reported and/or potential AEs (Section 8.1) and the characteristics of an observed AE (Section 8.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List TGR-1202

A Phase I clinical trial in patients with relapsed or refractory hematologic malignancies is ongoing evaluating escalating doses of single-agent TGR-1202. The following adverse events determined to be at least possibly related to TGR-1202 have been observed as of the cutoff date of 1 January 2014:

MedDRA system organ class	**Very Common ≥10%**	**Common ≥1% and <10%**	**Uncommon ≥0.1% and <1%**
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia		
Gastrointestinal disorders	Diarrhea Dyspepsia Nausea	Vomiting	
General disorders and administration site conditions	Fatigue	Asthenia Chills Malaise Oedema Peripheral Pyrexia	

Infections and infestations		Candidiasis Lung Infection	
Investigations		Blood Lactate Dehydrogenase Increased	
Metabolism and nutrition disorders	Decrease Appetite Dehydration	Hypokalaemia Hyponatraemia Hypernatraemia Hyperphosphataemia	
Musculoskeletal and connective tissue disorders		Muscular Weakness	
Nervous system disorders	Headache	Dizziness	
Respiratory, thoracic and mediastinal disorders	Cough	Hypoxia	
Skin and subcutaneous tissue disorders	Rash		

In addition to the preceding adverse events, the following adverse events occurred in patients administered TGR-1202 but were deemed by investigators to be unlikely related or not related to TGR-1202 therapy. Due to the low number of patients evaluable for safety at this time, however, TG Therapeutics cannot rule out these events occurring in future studies:

- **Blood and lymphatic system disorders**: anemia
- **Stomach and digestive system related disorders:** constipation, abdominal discomfort and pain, stomatitis
- **Liver Disorders:** elevated levels of certain liver enzymes
- **Brain and nerve related disorders:** dizziness, paresthesia
- **Kidney disorders:** elevated creatinine, elevated blood urea nitrogen levels, elevated phosphorus, hyperuricemia
- **Breathing and chest related disorders:** nasal congestion, pneumonia, dyspnea, upper respiratory tract infection
- **General disorders:** arthralgia, myalgia
- **Infections and Infestations:** infection

7.1.1.1 Precautions and Risks Associated with TGR-1202

Based on observations obtained from nonclinical toxicology studies in rodent and non-rodent species, the following adverse events may occur: changes in serum creatinine, changes in triglycerides, changes in total protein, changes in sodium, changes in chloride, reduction in leukocytes, reduction in lymphocytes, reduction in eosinophils, elevation in cholesterol, nausea, vomiting, mucoid stools, abnormal colored feces, soft stool, ocular discharge, and dehydration. Mild to moderate histopathological changes were noted in the liver at terminal necropsy at the highest doses of 750 mg/kg/day in mice and dogs. As a result, monitoring of liver enzymes in subjects receiving TGR-1202 is recommended (Current TGR-1202 IB).

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 TGR-1202, and instructions on how to manage patients.

7.1.2 Adverse Event List(s) Ibrutinib

Non-Hematologic Adverse Events in >10% of Patients with Mantle Cell Lymphoma (N=111)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administrative site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue	Musculoskeletal pain	37	1
	Muscle spasms	14	0

disorders	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea Cough Epistaxis	27 19 11	4 0 0
Metabolism and nutritional disorders	Decreased appetite Dehydration	21 12	2 4
Nervous system disorders	Dizziness Headache	14 13	0 0

Treatment-Emergent Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	All Grades (%)	**Grade 3 or 4 (%)**
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

For more information on adverse events associated with ibrutinib, see ibrutinib prescribing information.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. In addition to following the SAE reporting requirements for DFCI, other participating investigative sites will report SAEs to their respective IRB per the local IRB's policies and procedures.

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC.For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution must abide by the reporting requirements set by the DF/HCC.

Criteria for reporting to DFCI listed in section 7.5.3. The lead site will report external site SAEs to the DFCI IRB on the external site's behalf after review and approval by the overall PI. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.3 DF/HCC Expedited Reporting Guidelines

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

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed below.

DF/HCC Reportable AEs

- **CTCAE Grade 2 and Grade 3 Events** – that are *Unexpected* and there is a *Reasonable Possibility* that the *Adverse Event* is related to the study intervention.
- **CTCAE Grade 4 Events –** Report all events that are *Unexpected*. Events that are *Expected* and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB.
    - Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.
- **ALL CTCAE Grade 5 Events.**

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

Matthew Davids, MD, will be responsible for all communications with the FDA. Matthew

Davids, MD., will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Routine Adverse Event Reporting

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

7.6 Expedited Reporting to Hospital Risk Management

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 TGR-1202

8.1.1 Description

TGR-1202 is a highly specific and orally available PI3K delta inhibitor with nanomolar inhibitory potency, and several fold selectivity over the alpha, beta, and gamma isoforms. TGR-1202 is manufactured by Alembic Pharmaceuticals and supplied by TG Therapeutics, Inc. For this trial, TGR-1202 will be supplied in 200 mg tablets.

Preliminary pharmacokinetic analysis suggests TGR-1202 is rapidly absorbed (mean T_{max} ~2 hours), and displayed a Cycle 1, Day 1 half-life of ~9 hours. Steady state pharmacokinetics were achieved by Day 15 of dosing, with an estimated steady state half-life of ~50 hours observed. Kinetics were observed to be linear through 1200 mg QD dosing.

8.1.2 Form

TGR-1202 is available as a tablet with the following description:

- 200 mg: Light brown to brown color, oval tablets with "L474" debossed on one side and plain on the other side.

8.1.3 Storage and Stability

The Primary packaging is HDPE bottles each containing 30 tablets of 200 mg each. The HDPE bottles also contain a silica gel canister as a desiccant and cotton. A revision in primary packaging with inclusion of cotton was made, to fill the excess void space available in the bottles, leading to breakages of tablets observed during transportation. Store at 25°C.

Excursions permitted 15°C to 30°C.

The stability data on development and clinical batch shows that the drug substance has remained stable at all stability conditions for a period of 12 months.

8.1.4 Handling

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

8.1.5 Availability

Drug is provided by TG Therapeutics, Inc., New York, NY

8.1.6 Preparation

It is an oral drug, no preparation is required.

8.1.7 Administration

At each visit, patients will be dispensed sufficient TGR-1202 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.

TGR-1202 tablets will be self-administered by the patients. TGR-1202 will be administered orally once daily. Tablets should be taken at approximately the same time each day. TGR-1202 tablets should be swallowed whole with a full glass (approximately 8 ounces) of water. TGR-1202 tablets should NOT be crushed/opened or chewed. **Patients should be instructed to take TGR-1202 in the morning with food, preferably within 30 minutes of a meal.**

8.1.8 Ordering

Once the clinical trial site receives regulatory approval (IRB/IEB), and the Sponsor and/or Sponsor designee performs the Site Initiation Visit and inspection of pharmacy and determines the site to be officially open for enrollment, and once a patient is identified, a shipment of pre-determined quantity of TGR-1202 will be shipped to the clinical trial site.

Upon receipt of treatment supplies, the Pharmacist or the appropriate person of the site should update the accountability forms for TGR-1202.

If any abnormality on the supplied boxes is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee.

Study drug may be shipped from the investigational pharmacy to the patient's home according to each institution's policy and or SOP.

8.1.9 Accountability

The PI (or designee) is responsible for accountability of all used and unused trial drug supplies at the site.

The DF/HCC monitor will verify receipt of investigational product at the site during monitoring visit(s), and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All trial drug inventories must be made available for inspection by the monitor or representatives of the aforementioned and regulatory agency inspectors upon request.

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using a drug accountability form.

8.1.10 Destruction and Return

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented.

8.2 **Ibrutinib**

8.2.1 Description

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients

8.2.2 Form

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging. Study drug labels will contain information to meet the applicable regulatory requirements. Each bottle will contain a study specific label with a unique identification number.

8.2.3 Storage and Stability

The recommended storage condition for ibrutinib capsules is room temperature (15 to 25°C; 59 to 77°F). Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug preparation and handling.

8.2.4 Compatibility

Not applicable

8.2.5 Handling

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

Caution is required when handling ibrutinib. Pharmacists should follow standard procedures for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, provide treatment as necessary for physical exposure (skin washing) or inhalation (move to fresh air) and seek medical advice as necessary.

When ibrutinib capsules are distributed for self-administration, they should only be handled by the study subject. After handling capsules, the subject should wash their hands thoroughly. If someone who is not enrolled in a clinical trial involving ibrutinib swallows a capsule or inhales drug powder from a broken capsule of ibrutinib, they should contact the relevant Principal Investigator to determine whether safety monitoring is necessary. Capsules should always be stored in the container provided to the study subject.

8.2.6 Availability

Ibrutinib will be obtained by prescription, from commercial supply.

8.2.7 Preparation

It is an oral drug, no preparation is required.

8.2.8 Administration

Patients will be prescribed a sufficient ibrutinib drug supply until their next study visit. Ibrutinib tablets will be self-administered by the patients. Ibrutinib will be administered orally once daily. Tablets should be taken at approximately the same time each day, preferably in the evening. Ibrutinib capsules should be swallowed whole with a full glass (approximately 8 ounces) of water. Ibrutinib capsules should NOT be crushed/opened or chewed.

8.2.9 Ordering

See 8.2.6.

8.2.10 Accountability

Study drug compliance will be recorded by patients in a drug diary.

8.2.11 Destruction and Return

Patients should dispose of any unused ibrutinib through usual means such as returning it to

their local pharmacy for destruction.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

9.1.1 BH3 Profiling

BH3 profiling is a functional assay we previously developed that detects the proximity of CLL cells to the threshold of apoptosis (what we call 'priming') through interrogation of BCL-2 family members. To perform a BH3 profile, we add individual BH3-only peptides to gently permeabilized malignant cells and use FACS to measure the amount of mitochondrial depolarization induced by each peptide, as measured by cytochrome c release.

We hypothesize that patients whose cells undergo significant depolarization to BIM BH3 peptide (highly primed) will have superior clinical response to ibrutinib compared to patients whose cells undergo minimal BIM BH3 depolarization (unprimed).

9.1.2 Pharmacodynamic Markers

Pharmacodynamic markers will also be assessed to determine whether is hitting its proposed target *in vivo*. Viably frozen cells will be analyzed us phosphoflow cytometry to determine the levels of phospho-AKT and phospho-ERK compared to total AKT and ERK, respectively. These analyses will be confirmed in a subset of patients by Western Blot. In addition, current work has suggested that reduction in the cell proliferation marker Ki-67 in peripheral blood CLL cells occurs rapidly in patients treated with BCR pathway antagonists, and this may also be assessed in the Brown lab by phosphoflow cytometry in samples from patients on our study.

9.1.2.1 Collection of Specimen(s)

These assessments will be made on circulating CLL and MCL, when possible, cells from the peripheral blood drawn from patients at baseline. These samples will be drawn either at screening or prior to study drug dosing on Cycle 1, Day 1, If we have bone marrow aspirates available, we will also perform BH3 profiling to see whether the level of priming in CLL cells from these tissues is a better predictor of response than peripheral blood CLL cells. Bone marrow aspirate sample is requested if bone marrow procedure is performed as standard of care or as part of protocol schedule. In addition, saliva as a source of germline DNA will be collected prior to study initiation and may be collected more than once if inadequate specimen is obtained. All samples will promptly be delivered to the laboratory of Dr. Jennifer Brown (CLL patients)or Dr. Anthony Letai (MCL patients), where DNA will be extracted and then sent to the Broad Institute (Cambridge, MA) for whole exome sequencing.

After 1 week of treatment on Cycle 1, Day 8 (pre-dose), we will obtain another blood sample. We will compare the BH3 profile of this steady-state sample to a baseline sample, which will allow us to assess *in vivo* the short term change in apoptotic priming induced by these agents.

Finally, a peripheral blood will be collected from subjects at the time of disease progression, and the BH3 profile of these samples will be compared to subjects' baseline samples to help identify whether a change in anti-apoptotic protein dependence is observed as a possible mechanism of resistance. A bone marrow sample at confirmation of complete response will be obtained and sent to Integrated Oncology for minimal residual disease assessment, while blood from the same time point is analyzed at the laboratory of Jennifer Brown (CLL or SLL patients) or Antony Letai (MCL patients). For the patients that have obtained a complete response, we request that peripheral blood samples be obtained every 6 cycles thereafter until disease progression, removal from study, or death.

9.1.2.2 Handling of Specimens(s)

All peripheral blood and bone marrow samples obtained at DFCI will promptly be refrigerated and delivered the same day as soon as possible to the laboratory of Dr. Jennifer Brown or Dr. Anthony Letai at room temperature, where they will undergo Ficoll purification and then be viably frozen in FBS with 10% DMSO. The viably-frozen samples will be used for BH3 profiling assays (for detailed methods see (24).

Samples obtained from other institutions may either undergo Ficoll purification locally and then be viably frozen in FBS with 10% DMSO prior to shipment, or may be kept as whole blood and shipped on ice as soon as possible to Dr. Brown's or Dr. Letai's lab.

9.1.2.3 Shipping of Specimen(s)

CLL/SLL patient samples obtained from sites other than DFCI should be shipped directly to Dr. Brown's lab at the following address:

Stacey Fernandes, Principal Research Technician
CLL Center, J. Brown lab
Dana Farber Cancer Institute
1 Jimmy Fund Way, JFB 426
Boston, MA 02115, U.S.A.
617-632-5828 (phone)
Email: Stacey_Fernandes@dfci.harvard.edu.

MCL patient samples obtained from sites other than DFCI should be shipped directly to Dr. Letai's lab at the following address:

Tim Lehmberg, Research Technician
Dana Farber Cancer Institute
1 Jimmy Fund Way, Mayer 545
Boston, MA 02115, U.S.A.
Email: TimothyZ_Lehmberg@dfci.harvard.edu

The study sample requisition form provided to the site should be included in every shipment and an email notification with the package tracking number emailed the Research Project Manager.

The blood and bone marrow samples that are requested to confirm complete response for minimal residual disease will be sent to Genzyme Genetics (LabCorp Specialty Testing Group/Integrated Oncology) for analysis by flow cytometry. These samples will be shipped alongside the Integrated Oncology/LabCorp requisition form (to be provided) ambient priority overnight to:

Genzyme/LabCorp Specialty Testing Group
521 West 57th Street
New York, NY 10000

9.1.2.4 Site(s) Performing Correlative Study

All sites will be encouraged to provide the correlative samples for analysis, as feasible. While the goal of the biomarkers is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, not perform, or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc). Therefore, depending on the results obtained during the study, sample collection/analysis may be omitted at the discretion of the PI.

9.1.2.5 Sample Collection

Sample Time Point	Container [3]	Sample Type	Shipping Method[1,2]	Recipient[4,7]
Baseline or C1D1 Predose	6x6mL Green 1x6ml Red	Peripheral Blood	Fridge pack same day	Brown/Letai Lab
	1x6ml Green	Bone Marrow Aspirate	Fridge pack same day	Brown/Letai Lab
	Oragene Kit	Saliva	Ambient same day	Brown/Letai Lab
	2x10ml Purple* 1x6ml Green*	Peripheral Blood	Fridge pack same day	Integrated Oncology
C1D8 Predose	6x6mL Green 1x6ml Red	Peripheral Blood	Fridge pack same day	Brown/Letai Lab
Disease Progression/End of Treatment	6x6mL Green 1x6ml Red	Peripheral Blood	Fridge pack same day	Brown/Letai Lab
	1x6ml Green[6]	Bone marrow Aspirate		
Confirmation of Complete Response	6x 6mL Green 1x6ml Red	Peripheral Blood	Fridge pack same day	Brown/Letai Lab
	1x6ml Green[6]	Bone Marrow Aspirate	Fridge pack same day	Brown/Letai Lab
	1x6mL Green[5,6**]	Bone Marrow Aspirate	Fridge pack same day	Integrated Oncology
Every 6 Cycles[8] from C1D1	6x6mL Green 1x6ml Red	Peripheral Blood	Fridge pack same day	Brown/Letai Lab

[1]For outside sites, local lab may also Ficoll purify sample then viably freeze in Fetal Bovine Serum with 10% DMSO prior to shipment on dry ice.
[2]For DFCI sites: refrigerate and deliver as soon as possible same day to Jennifer Brown lab
[3]Green=Sodium Heparin Tube; Red= No additive; Purple = K2EDTA; Oragene kit provided by DFCI
[4] Requisition form and shipping instructions for Integrated Oncology provided by lead site
[5] Only required to confirm CR in patients who had a positive marrow at baseline
[6] Only for patients who had a positive marrow at baseline
[7] CLL/SLL patient correlatives are sent to Dr. Jennifer Brown's Lab; MCL patient correlative samples are sent to Dr. Anthony Letai's Lab, except for Oragene kits, all of which go to the CLL lab of Dr. Brown
[8] Requested for all patients who remain on study; ie: stable disease to morphologic/radiographic CR eg: Cycles 6, 12, 18, 24, 30, 36 etc.
*Not required for MCL patients, or patients who have already enrolled on DFCI Trial 99-224
** Not required for MCL patients

10. **STUDY CALENDAR**

Baseline evaluations / laboratory tests should be conducted within 21 days prior to C1D1. Scans used to identify measurable/evaluable disease are required to be done within 30 days prior to C1D1. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. During cycles 12 and beyond, patients will be seen every 3 cycles (84 days +/- 7 days). After Cycle 36, participant have the option to return to the main research institution every 6 cycles (168 days +/-14 days) for full evaluation only if they are being followed every 3 cycles by a local oncologist. For full list of required assessments, please refer to section 5.4.10. After Cycle 15, scans will be performed approximately every 6 cycles (168 +/- 14 days) or more frequently, until C36 at which point they may be performed at the investigator's discretion until removal from treatment. Survival follow up should occur approximately every 3 cycles for up to 2 years, until death or next CLL/MCL-directed therapy, whichever occurs first.

Cycle = 28 days	**Screening**	**Cycle 1** (+-3 Days)				**Cycle 2** (+-3 Days)		**Cycles –3-6** (+-3 Days)	**Cycles 8+** (*Every 2 cycles until C12, then every 3 cycles until C36 or beyond* [11])	**Disease Progression/End of Treatment**[9,10]	**Follow Up** *(every 3 cycles for up to 2 years until new therapy, death, or withdrawal)*
Procedure \ Days	**-21-0**	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1		
TGR-1202 Dose		Daily Dosing - Days 1 – 28									
Ibrutinib Dose		Daily Dosing - Days 1 – 28									
Survival Status[12]											X[12]
Informed consent	X										
Medical history	X	X	X	X	X	X	X	X	X	X	
Serum Pregnancy test	X*										
Physical examination	X	X	X	X	X	X	X	X	X	X	
Vital signs (pulse rate, BP, temperature)	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X										
BM aspirate /biopsy [1, 2, 3]	X[3]							X[2,3]		X[2,3]	X[2,3]
SPEP + Immunoglobulins [4]	X							X			
ECOG performance status	X	X	X	X	X	X	X	X	X	X	
EKG	X										
Serology: HIV, HCV, HBV	X										
CT scan (+/- 7 days)	X							X[5]	X[5,6]	X	X[5,6]
Hematology	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	
PT/PTT/INR	X					X					
FISH Analysis / IGHV status/TP53/Zap70 [7]	X										
Correlative studies	X[8,3]	X	X							X[3]	

Cycle = 28 days	**Screening**	**Cycle 1** (+-3 Days)				**Cycle 2** (+-3 Days)		**Cycles –3-6** (+-3 Days)	**Cycles 8+** (***Every 2 cycles until C12, then every 3 cycles until C36 or beyond*** [11]	**Disease Progression/End of Treatment**[9,10]	**Follow Up** ***(every 3 cycles for up to 2 years until new therapy, death, or withdrawal)***
Procedure \ Days	**-21-0**	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1		
Adverse Event Evaluation	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication		X	X	X	X	X	X	X	X	X	

[1] Unilateral bone marrow aspirate and/or biopsy required within 90 days prior to Day 1 of Cycle 1

[2] Only in patients who had a positive bone marrow prior to study initiation who achieve a radiographic CR, to confirm CR.

[3] Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care, or as part of protocol schedule

[4] SPEP required at baseline and then at Cycle 3 and 6, 8, 10, 12, then every 3 cycles until Cycle 36, and every 6 cycles thereafter only if M protein detected at baseline; If no M protein detected at baseline, IgG, IgA, IgM to be checked Cycle 3 and 6, 8, 10, 12, then every 3 cycles until Cycle 36, and every 6 cycles thereafter (B2M only at baseline)

[5] Just prior to cycle 3, then just prior to cycles 6, 10 and 15 (eg: C2D28, C5D28, C9D28, C14D28 +/- 7 days)

[6] After C14D28 scans, CT scans should occur approximately every 6 cycles until C36 (+/- 14 days), then per investigator discretion thereafter

[7] FISH for both CLL/SLL and MCL are to be done locally- IGHV, TP53 and Zap70 for CLL/SLL patients only (Integrated Onc.)

[8] Baseline correlative studies may be obtained either at the screening visit or prior to study drug administration on C1D1.

[9] End of treatment should be the next visit following a cycle after study drug was administered (within 3 days).

[10] Patients are to be followed for survival and response every 3 months for up to two years or until death or other CLL/MCL directed therapy

* Within 3 days of Day 1 / Cycle 1

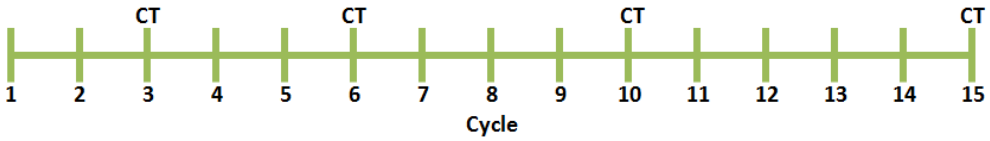
[11] After cycle 36, participants may return to the main study site every 6 cycles (168 days+/-14 days) if they are being followed by a local hematologist/oncologist in the interim q3 cycles (84 +/-14 days). No study specific assessments need occur at the interim visits. Please see section 5.4.10 for additional information . Those who remain at the main research institution for all visits will continue to be seen every 3 cycles.

[12] Survival data may be collected by phone if necessary

* Within 3 days of Day 1 / Cycle 1

11. **MEASUREMENT OF EFFECT**

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, the first efficacy assessment should be approximately 8 weeks after Cycle 1/Day 1 (+/- 7 days) and then just prior to cycles 6, 10 and 15. After cycle 15, efficacy assessments should occur at least every 6 cycles (168 +/- 14 days) until Cycle 36, where scans may be performed per investigator discretion.



11.1 **Antitumor Effect**

Assessment of lymphoma response (CR, PR or SD) and disease progression will be evaluated as outlined in the schedule of events, according to the Revised Response Criteria for Malignant Lymphoma for MCL and SLL patients (26) and for CLL patients, the IWCLL Response Criteria (27) as modified by (28).

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on Cycle 1/Day 1.

Evaluable for objective response. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least two dimensions as ≥1 cm with spiral CT scan. All tumor measurements should be recorded in centimeters. For CLL, patients without measurable lymph node disease will have measureable disease include lymphocytosis ≥ 5,000/µL and/or bone marrow involvement.

Non-measurable disease. All other lesions (or sites of disease) including small lesions, (<1 cm using spiral CT scan) are considered non-measurable disease. Bone lesions, ascites, pleural/pericardial effusions, lymphangitis, and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 6 lesions total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest SPD

diameter), and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A baseline sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 0.5cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size of a measurable lesion should be twice the slice thickness.

11.2 **Response Criteria**

See Appendix A for SLL and MCL. See Appendix B for CLL.

11.2.1 Radiographic Response Review

Radiology will be centrally reviewed by the DF/HCC Tumor Imaging Metrics Core (TIMC).

Each participating site will be responsible for assuring review and confirmation of response as per standard review guidelines at that center. Patients who achieve an objective response may have scans collected and reviewed by independent radiology set up by the Sponsor.

11.2.2 Nodal Partial Response (nPR)

It is anticipated that many patients on this study, particularly in the CLL arm, will experience increased lymphocytosis after starting on the study drugs. This is a well-known phenomenon that is a class effect of the BCR inhibitor drugs. In clinical experience, these patients appear to derive a similar clinical benefit from BCR inhibitors as patients who achieve a traditional PR. Therefore, a revision to the IWCLL criteria was proposed and is now widely recognized. As per Cheson et al., 2012, patients who achieve a radiographic PR but continue to have a

lymphocytosis with >5,000 B-lymphocytes per μL where the absolute lymphocyte count has not decreased by 50% or more compared to baseline are considered to have a nodal partial response, also known as PR with lymphocytosis.

11.2.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria as per the MCL and CLL established criteria used in this study (See Appendix A and B).

11.2.4 Duration of Response

Duration of response is defined as the time from documentation of a response to treatment to the first documentation of documentation of tumor progression or death due to any cause whichever comes first. Duration of the response will be summarized using n (sample size), mean, standard deviation, median, minimum, and maximum for the responders.

11.2.5 Progression-Free Survival

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

12. **DATA REPORTING / REGULATORY REQUIREMENTS**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0

12.1 **Data Reporting**

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT. Data should be entered within 14 business days of the corresponding visit and within 14 business days of the end of a cycle for any forms to be completed per cycle.

12.2 **Data Safety Monitoring**

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 **Multicenter Guidelines**

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. **STATISTICAL CONSIDERATIONS**

This is a multi-center Phase I/Ib study evaluating the safety of the novel PI3k delta inhibitor TGR-1202 in combination with ibrutinib in patients with relapsed or refractory CLL or MCL. The primary endpoint of this study is to determine the maximum tolerated dose (MTD) in each disease group separately.

13.1 **Determining MTD**

This is a 3+3 design with four doses of TGR-1202 to be considered to determine MTD: 200mg (dose level -1), 400 mg (dose level 1, starting dose), 600 mg (dose level 2), and 800 mg (dose

level 3). Dose limiting toxicities (DLTs) were defined in section 5.6.3.

A cohort of 3 patients will enter at each dose level. If no DLT is seen in the first 3 eligible patients at dose level 1 or 2, a dose escalation will take place. If no DLT is seen in the first 3 eligible patients at dose level 3 or -1, 3 additional patients will be treated at that dose level. If 2 or more of the 3 eligible patients experience a DLT at dose level 1, 2, or 3, the next cohort of 3 patients will be treated at the next lower dose level, unless 6 patients have already been treated at that dose level. If 2 or more of the first 3 eligible patients experience a DLT at dose level -1, the study will be terminated early. If 1 of the first 3 patients experiences a DLT then 3 additional patients will be treated at that dose level. If there is no DLT in the 3 additional patients then dose escalation will take place. If this is dose level 3 or -1, then this dose is the MTD. If 1 or more of the 3 additional patients experience(s) DLT then the MTD is considered exceeded, and 3 more patients are treated at the next lower dose, unless 6 patients have already been treated at that dose level. If this is dose level -1, the study will be terminated early.

A minimum of six patients must be evaluated at the highest tolerated dose level, and fewer than 2 patients in 6 should experience DLT.

Table 5 shows the probability of escalation under various true DLT rates. With this design, there is 91% probability of dose escalation if the true rate of DLT is 10% and 17% probability of escalation if the true DLT rate is 50%.

Table 5: probability of dose escalation

True Rate of DLT	Prob. of Escalation
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

13.2 **Phase Ib**

Once the MTD is established, an additional 12 eligible patients in each disease group will be treated at the MTD level to further evaluate the safety of TGR-1202 in combination of ibrutinib. The estimation of toxicity rate will be based on these 12 additional patients. With 12 patients, the 90% confidence interval of the toxicity rate will be within ±25%.

13.3 **Accrual**

The sample size will approximately range from 4-30 eligible patients in each disease, depending on the observance of DLTs and the number of dose levels tested. Based on the current practice, we anticipate that the accrual rate will be approximately 2-3 patients per month per disease.

13.4 **Analysis Plan for Secondary Objectives**

The secondary objectives include assessment of the overall response rate, nodal partial response rate, progression-free survival, and duration of response. Due to the exploratory nature, the analysis for secondary endpoints will largely be descriptive. Response rate and duration of response will be summarized descriptively and the Kaplan Meier method will be used to estimate the median progression-free survival time and progression-free survival. A similar descriptive analysis will be performed for laboratory correlative studies of BH3 profiling and pharmacodynamic markers such as phosphorylated levels of AKT, BTK, and ERK, as well as Ki-67 level. If feasible, association between clinical response and laboratory endpoints will be explored.

14. **PUBLICATION PLAN**

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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16. APPENDIX A RECOMMENDATIONS FOR INITIAL EVALUATION, STAGING, AND RESPONSE ASSESSMENT OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE LUGANO CLASSIFICATION

(CHESON ET. AL. 2014)

Revised Criteria for Response Assessment

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

Response and Site	PET-CT–Based Response	CT-Based Response
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and

Response and Site	PET-CT–Based Response	CT-Based Response
		An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

- ↵* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not

meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

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

APPENDIX B CHRONIC LYMPHOCYTIC LEUKEMIA RESPONSE DEFINITION (HALLEK ET AL. 2008)

Assessment of response should include a careful physical examination and evaluation of the blood and marrow.

Complete Response: (CR)	***CR requires all of the following criteria as assessed at least 2 months after completion of therapy:*** 1. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/μL). 2. Absence of significant lymphadenopathy (e.g., lymph nodes >1.5 cm in diameter) by physical examination. 3. No hepatomegaly or splenomegaly by physical examination and CT. 4. Absence of constitutional symptoms. 5. Blood counts above the following values: • Neutrophils >1.5 x 10^9/L (1500/μL) without need for exogenous growth factors. • Platelets >100 x 10^9/L (100 000/μL) without need for exogenous growth factors. • Hemoglobin >110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin. **For patients in clinical trials, a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed above a-e demonstrate that a CR has been achieved.** To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. In some cases, lymphoid nodules can be found, which often reflect residual disease. These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician.

	In clinical trials aiming at maximizing the CR rate, the quality of the CR should be assessed for MRD by flow cytometry or by immunohistochemistry. **A controversial issue is how best to categorize the response of patients who fulfill all the criteria for a CR (including the marrow examinations described above) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity.** We recommend that these patients be considered as a different category of remission: CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (described above) should be performed with scrutiny and not show any clonal infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual or with noncytopenic CR.

Partial Response: (PR)	***To define a PR (partial remission): at least two of the criteria of Group A plus one of the criteria of Group B have to be met. The parameters below should be documented for no less than 2 months. Constitutional symptoms persisting for >1 month should be recorded.*** ***Group A*** a. Decrease in the number of blood lymphocytes by 50% or more from the value before therapy. b. Reduction in lymphadenopathy (by PE and CT scans) as defined by the following: • A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy. • No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (<2 cm), an increase of less than 25% is not considered to be significant. c. Reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan. ***Group B*** d. Blood count should show one of the following: • Neutrophils >1.5 x 10^9/L (1500/μL) without need for exogenous growth factors. • Platelet count >100 x 10^9/L (100 000/μL) or 50% improvement over baseline without need for exogenous growth factors. • Hemoglobin >110 g/L (11.0 g/dL), or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

Chronic Lymphocytic Leukemia Response Definition (Hallek et al. 2008) (continued)

Progressive Disease: (PD)	***Progressive disease during or after therapy is characterized by at least one of the following:*** a. Lymphadenopathy: Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse. Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed: • Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. • An increase by 50% or more in greatest determined diameter of any previous site. b. An increase in the previously noted enlargement of the liver or spleen by 50% or more, or the de novo appearance of hepatomegaly or splenomegaly. c. An increase in the number of blood lymphocytes by 50% or more, with at least 5000 B-lymphocytes per µL. d. Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy. e. Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL • *During therapy:* Cytopenias may occur as a side effect of many therapies. During therapy, cytopenias cannot be used to define disease progression. • *After treatment:* The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by >20 g/L (2 g/dL) or to <100 g/L (10 g/dL), or by a decrease of platelet counts by >50% or to <100 x 10^9/L (100,000/µL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.
Stable Disease: (SD)	Patients who have not achieved a CR, PR, or nPR and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a non-response).
Nodular Partial Response (nPR)	As per Cheson et al., 2012, patients who achieve a radiographic PR but continue to have a lymphocytosis with >5,000 B-lymphocytes per µL are considered to have a nodular partial response, also known as PR with lymphocytosis, due to the fact that they appear to derive a similar clinical benefit from BCR inhibitors as patients who achieve a traditional PR.

Source: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008;111:5446-56.

APPENDIX C CONTRACEPTIVE GUIDELINES AND PREGNANCY

Women Not of Childbearing Potential are Defined as Follows:

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

Contraceptive Guidelines for Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for additional 4 weeks after study drug discontinuation. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that patient.

4. Use of a combination of any two of the following (a+b):
    a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- Oral contraception, injected or implanted hormonal methods are not allowed as ibrutinib potentially decreases the effectiveness of hormonal contraceptives.
- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal

- Cervical shield

Women of child-bearing potential must have a negative serum or urine pregnancy test ≤ 72 hours prior to initiating treatment.

Fertile Males:
Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, for additional 4 weeks after study drug discontinuation, and should not father a child in this period.

Pregnancies
To ensure patient safety, each pregnancy in a patient on study treatment must be reported to TG Therapeutics Inc. within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to TG Therapeutics Inc. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug and reported by the investigator to TG Therapeutics Inc. Any SAE experienced during pregnancy must be reported on the SAE Report Form.
Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

APPENDIX D IWCLL GRADING SCALE FOR HEMATOLOGIC TOXICITY IN CLL STUDIES

Grade	Decrease in Platelets¢ or Hb‡ (nadir) from Pretreatment Value, %	Absolute neutrophil count/µL (nadir)§
0	No change to 10%	≥2000
1	11% - 24%	≥1500 and <2000
2	25% - 49%	≥1000 and <1500
3	50% - 74%	≥ 500 and <1000
4	≥75%	<500

Grades: 1, mild; 2, moderate; 3 severe; 4 life-threatening; 5 fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

¢Platelet decrease, must be below normal levels for grades 1 to 4 at any level of decrease, the platelet count is <20X 10^9/L (20,000/µL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20 X 10^9/L [20 000/µL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡ Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§ If the absolute neutrophil count (ANC) reaches <1X 10^9/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was< 1X 10^9/L (1000/µL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

APPENDIX E: 14-396 MCL STUDY PARTICIPANT SELF-ADMINISTERED DRUG DIARY

PATIENT INSTRUCTIONS: Take your medications exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking.
Both TRG-1202 and ibrutinib should be kept in the provided bottles. Store drugs at room temperature.

TGR-1202:

- TGR-1202 should be taken by mouth once per day**, preferably in the morning**. TGR-1202 should be taken with food, preferably within 30 minutes of a meal and with a full glass of water (approximately 8 ounces).
- Do not split or crush tablets or empty into any food or drink for oral ingestion. Tablets must be swallowed whole.
- If you vomit after taking TGR-1202, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If a dose is missed and it is less than 4 hours from usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing the following day. If you miss a dose, record "0" for **Number Taken** on the next page.
- If you accidentally take an extra dose during a day skip the next day's dose and record the extra dose on the next page.
- Please bring any unused TGR-1202 tablets, all empty TGR-1202 containers and diary to your next visit.

Ibrutinib:

- Ibrutinib should be taken by mouth once per day, **preferably in the evening** and can be taken with or without food. Capsules should be swallowed intact with 8 ounces of water (approximately 8 ounces).
- Do not consume grapefruit, grapefruit juice or Seville oranges. Do not take fish oil or vitamin E supplements. Consult your doctor before making any changes to medications or supplements.
- If a dose is missed, it can take it as soon as possible on the same day and you should take dose at the normally scheduled time the next day.
- If you vomit drug, please record this in diary as a missed dose and do not take another dose of drug that day.

<table>
<tr><th colspan="3">FOR CLINIC USE ONLY:</th></tr>
<tr><td rowspan="5">• Give patient all 2 pages of Drug Diary stapled together. Provide one diary per cycle (28 days).
• Complete patient identifiers and medical team contact information on page 2.
• Complete correct dose levels for TGR-1202 and Ibrutinib therapy on page 2.
• When patient returns pill bottles and diary perform a TGR-1202 pill count and record adherence information in the box to the right.</td><td colspan="2">Staff Initials:</td></tr>
<tr><td>Date Dispensed:</td><td>Date Returned:</td></tr>
<tr><td># TGR-1202 tablets dispensed:</td><td># TGR-1202 tablets returned:</td></tr>
<tr><td colspan="2"># TGR-1202 tablets that should have been taken:</td></tr>
<tr><td colspan="2">Discrepancy Notes:</td></tr>
</table>

APPENDIX E: MCL 14-396 STUDY PARTICIPANT

SELF-ADMINISTERED DIARY

Participant Identifier: _____ Cycle #: _____
Your MD _____
Phone _____
Your RN _____
Phone _____

STUDY DRUG INSTRUCTIONS:
Take the following medications as indicated below. Record the dose of each medication on the chart to the right after taking each day.

TGR-1202 dose:

☐ 1 x 200 mg tablets by mouth on Days 1-28 (200 mg)
☐ 2 x 200 mg tablets by mouth on Days 1-28 (400 mg)
☐ 3 x 200 mg tablets by mouth on Days 1-28 (600 mg)
☐ 4 x 200 mg tablets by mouth on Days 1-28 (800 mg)

Ibrutinib:

☐ 4 x 140 mg capsules by mouth on Days 1-28 (560 mg)

Patient
Signature:_____Date:_____

Study Staff
Signature:_____Date:_____

	Date	TGR- 1202		Ibrutinib		Comments
		Number Taken	Time Taken	Number Taken	Time Taken	
Ex.	11/2/14	1	8:00 AM	1	8:00 PM	
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
Day 6						
Day 7						
Day 8						
Day 9						
Day 10						
Day 11						
Day 12						
Day 13						
Day 14						
Day 15						
Day 16						
Day 17						
Day 18						
Day 19						
Day 20						
Day 21						
Day 22						
Day 23						
Day 24						
Day 25						
Day 26						
Day 27						
Day 28						

APPENDIX F: 14-396 CLL/SLL STUDY PARTICIPANT SELF-ADMINISTERED DRUG DIARY

PATIENT INSTRUCTIONS: Take your medications exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking.

Both TRG-1202 and ibrutinib should be kept in the provided bottles. Store drugs at room temperature.

TGR-1202:

- TGR-1202 should be taken by mouth once per day, **preferably in the morning**. TGR-1202 should be taken with food, preferably within 30 minutes of a meal and with a full glass of water (approximately 8 ounces).
- Do not split or crush tablets or empty into any food or drink for oral ingestion. Tablets must be swallowed whole.
- If you vomit after taking TGR-1202, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If a dose is missed and it is less than 4 hours from usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing the following day. If you miss a dose record "0" for **Number Taken** on the next page.
- If you accidentally take an extra dose during a day skip the next day's dose and record the extra dose on the next page.
- Please bring any unused TGR-1202 tablets, all empty TGR-1202 containers and diary to your next visit.

Ibrutinib:

- Ibrutinib should be taken by mouth once per day, **preferably in the evening** and can be taken with or without food. Capsules should be swallowed intact with 8 ounces of water (approximately 8 ounces).
- Do not consume grapefruit, grapefruit juice or Seville oranges while taking ibrutinib. Do not take fish oil or vitamin E supplements. Consult your doctor before making any changes to medications or supplements.
- If a dose is missed, it can take it as soon as possible on the same day and you should take dose at the normally scheduled time the next day.
- If you vomit drug, please record this in diary as a missed dose and do not take another dose of drug that day.

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<tr><td>Date Dispensed:</td><td>Date Returned:</td></tr>
<tr><td># TGR-1202 capsules dispensed:</td><td># TGR-1202 capsules returned:</td></tr>
<tr><td colspan="2"># TGR-1202 capsules that should have been taken:</td></tr>
<tr><td colspan="2">Discrepancy Notes:</td></tr>
</table>

APPENDIX F: 14-396 CLL/SLL STUDY PARTICIPANT SELF-ADMINISTERED DIARY

Participant Identifier: _____ Cycle #: _____
Your MD _____
Phone _____
Your RN _____
Phone _____

STUDY DRUG INSTRUCTIONS:
Take the following medications as indicated below. Record the dose of each medication on the chart to the right after taking each day.

TGR-1202 dose:

☐ 1 x 200 mg tablets by mouth on Days 1-28 (200 mg)
☐ 2 x 200 mg tablets by mouth on Days 1-28 (400 mg)
☐ 3 x 200 mg tablets by mouth on Days 1-28 (600 mg)
☐ 4 x 200 mg tablets by mouth on Days 1-28 (800 mg)

Ibrutinib:

☐ 3 x 140 mg capsules by mouth on Days 1-28 (420 mg)

Patient Signature:_____Date:_____

	Date	TGR- 1202		Ibrutinib		Comments
		Number Taken	Time Taken	Number Taken	Time Taken	
Ex.	11/2/2014	1	8:00 AM	1	8:00PM	
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
Day 6						
Day 7						
Day 8						
Day 9						
Day 10						
Day 11						
Day 12						
Day 13						
Day 14						
Day 15						
Day 16						
Day 17						
Day 18						
Day 19						
Day 20						
Day 21						
Day 22						
Day 23						
Day 24						
Day 25						
Day 26						
Day 27						
Day 28						

Study Staff Signature:_____Date:_____

APPENDIX G PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX H THE NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

The following table presents the NYHA classification of cardiac disease:

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

DFCI IRB Protocol #: 14-396

APPENDIX I: DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA SAFETY MONITORING PLAN

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures..

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines. The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC

Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. QACT also coordinates quality assurance efforts related to multi-center clinical research.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, **Matthew Davids, MD** will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC QACT.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.

- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis

about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any

information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC QACT case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

See **Sections 4.3 and 4.4** of the protocol**.**

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, QACT requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms “violation”, “deviation” and “exception” to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution’s IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in **Section 7** of the protocol.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC QACT develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC QACT provides a web based training for eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC QACT Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in **Section 8** of the protocol.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the QACT provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution.

The DF/HCC Lead Institution will implement on-site as well as virtual monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. At a minimum, the DF/HCC Lead Institute, or designee, will monitor each participating site twice a year while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits, then a second monitoring visit may not be necessary.

Monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management. Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site teleconferences at least monthly. The Lead Institution will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or secondary endpoints.

On-Site Monitoring: On-site monitoring will occur ideally once per year while the site is actively enrolling patients, budget permitting. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled. On site monitoring visits can be supplemented with virtual monitoring assessments, provided that the minimum monitoring frequencies are adhered to.

Virtual Monitoring: The Coordinating Center will request source documentation from Participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Due to the small patient population, the accrual minimum requirement is at least 1 patient per site annually.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the QACT, assuming at least three participants have been treated on protocol at the site, or at the discretion of the DF/HCC Sponsor. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC QACT

per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX J: INHIBITORS AND INDUCERS OF CYP3A

Inhibitors and inducers of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR TELITHROMYCIN **Moderate inhibitors:** Aprepitant Erythromycin diltiazem Fluconazole grapefruit juice Seville orange juice Verapamil **Weak inhibitors:** Cimetidine **All other inhibitors:** Amiodarone NOT azithromycin Chloramphenicol Boceprevir Delavirdine diethyl-dithiocarbamate Fluvoxamine Gestodene Imatinib Mibefradil Mifepristone Norfloxacin Norfluoxetine star fruit Telaprevir Troleandomycin	Carbamazepine Efavirenz Nevirapine Barbiturates Carbamazepine Glucocorticoids Modafinil Oxcarbazepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone