COLUMBIA UNIVERSITY MEDICAL CENTER

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TITLE: **Phase Ib Study of Carfilzomib and a PI3K Delta Inhibitor TGR-1202 in the Treatment of Patients with Relapsed or Refractory Lymphoma**

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SUMMARY

Title:

Phase Ib Study of Carfilzomib and a PI3K Delta Inhibitor TGR-1202 in the Treatment of Patients with Relapsed or Refractory Lymphoma

Study Design:

This is an open label, dose-escalation phase I study followed by a phase Ib expansion phase.

The primary objective of the phase I is to determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of the combinations of TGR-1202 and carfilzomib in patients with relapsed and refractory (R/R) non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). The safety and toxicity of this combination will be evaluated throughout the entire study.

If the combination of TGR-1202 and carfilzomib is found to be feasible and an MTD is established, the phase Ib part of the study will be initiated.

The phase Ib part of the study will be conducted in patients with peripheral T cell lymphoma (PTCL) and C-MYC positive (30% by IHC) diffuse large B cell lymphoma (DLBCL).

Objectives:

Phase I:

Primary Objectives

- Determine the maximum tolerated dose (MTD), maximally administered dose (MAD), and dose limiting toxicity (DLT) of the combination of TGR-1202 and carfilzomib.
- Evaluate the safety and toxicity of the combination of TGR-1202 and carfilzomib.

Secondary Objectives

- Describe the maximum number of cycles received
- Describe the number of dose delays and dose reductions at the MTD

- Describe the anti-tumor activity of the combination
- Evaluate the objective response rate (ORR), progression free survival (PFS), and duration of response (DOR) of the study population.
- Evaluate pharmacodynamic markers of drug effect in paired tissue biopsies (pre- and post-treatment) including gene expression profiling (GEP) and immunohistochemistry (IHC).
- Establish the pharmacokinetic profile for TGR-1202 and carfilzomib when given as a combination in Cycle 1.

Phase Ib:

Primary Objectives

- Evaluate the safety and toxicity of the combination of TGR-1202 and carfilzomib at the MTD dose level in patients with R/R PTCL and C-MYC positive DLBCL.

Secondary Objectives

- Estimate the ORR (complete + partial response) of the combination of TGR-1202 and carfilzomib in patients with R/R PTCL and C-MYC positive DLBCL.
- Estimate the DOR and PFS of the combination in patients with R/R PTCL and CMYC positive DLBCL.

Target Population

Phase I: Patients with R/R NHL and HL.
Phase Ib: Patients with relapsed or refractory R/R PTCL and C-MYC positive DLBCL .

Inclusion Criteria

- Phase I: Patients with relapsed or refractory Hodgkin lymphoma or non-Hodgkin lymphoma. Patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are also eligible. In addition, patients with NHL other than diffuse large

B cell lymphomas (DLBCL) must have received at least 2 prior therapies. Patients with DLBCL and HL will be eligible if there is no available standard therapy.

- Phase Ib: Patients must have histologically confirmed R/R PTCL or C-MYC positive DLBCL (as defined by WHO criteria and IHC staining of C-MYC). The patients with PTCL or DLBCL will be eligible if there is no available standard therapy.
- Must have received front-line chemotherapy. No upper limit for the number of prior therapies. Patients may have relapsed after prior autologous stem cell transplant or allogeneic stem cell transplant.
- Evaluable Disease in the Phase I, and measurable disease for the phase Ib study as defined in Section 11 in the Phase Ib.

 Age ≥18 years

- ECOG performance status ≤ 2
- Patients must have adequate organ and marrow function as defined below:
  - absolute neutrophil count ≥1,000/dL
  - platelets ≥75,000
  - total bilirubin ≤1.5X institutional limits

    Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN; aPTT, PT not to exceed 1.2 × ULN
  - AST(SGOT)/ALT(SGPT) ≤2.0X institutional upper limit of normal ○ Serum creatinine within normal institutional limits

    ▪ OR
  - Measured creatinine clearance ≥50 mL/min/for patients with creatinine levels above institutional normal. ○ Left ventricular ejection fraction (LVEF) ≥50% as defined by ECHO or MUGA.
- Negative urine or serum pregnancy test for females of childbearing potential. All females of childbearing potential must use an effective barrier method of contraception (either an IUD or double barrier method using condoms or a diaphragm plus spermicide) during the treatment period and for at least 1 month thereafter. Male subjects should use a barrier method of contraception during the treatment period and for at least 3 months thereafter.

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

Exclusion Criteria

- Prior Therapy
    - Exposure to chemotherapy or radiotherapy within 2 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier. ○ Systemic steroids that have not been stabilized (≥ 5 days) to the equivalent of

      ≤10 mg/day prednisone prior to the start of the study drugs. ○

    No other concurrent investigational agents are allowed.
- Central nervous system metastases, including lymphomatous meningitis will be allowed in the phase II study, but will not be allowed in the phase I.
- History of allergic reactions to TGR-1202 or carfilzomib.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant women
- Nursing women
- Active concurrent malignancy (except non-melanoma skin cancer, carcinoma in situ of the cervix, low risk prostate cancer). If there is a history of prior malignancy, the patient must be disease-free for ≥ 2 years.
- Patients with a low grade lymphoma or CLL and a concurrent high grade lymphoma transformed from the low grade lymphoma or CLL will be eligible.
- Patients known to be Human Immunodeficiency Virus (HIV)-positive
- Patients with active hepatitis A, hepatitis B, or hepatitis C infection
- Concomitant use of CYP3A4 inhibitors (see Appendix 2) Significant cardiac abnormalities such as:
    - Myocardial infarction within 6 months of C1D1;
    - An ECG recorded at screening showing evidence of cardiac ischemia (ST depression of ≥2 mm, measured from isoelectric line to the ST segment). If in any doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present;

- Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix 4) and/or ejection fraction <50% defined by ECHO and MUGA;

- A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter-defibrillator (AICD).

Treatment Plan

Patients will be treated with TGR-1202 and carfilzomib administered as follows: TGR-1202 from Days 1-21; and carfilzomib administered intravenously on Days 1, 8, and 15 of a 28-day cycle (Tables 1 & 2).

In the Phase I study 3 subjects per cohort will be enrolled in each of the 2 escalating cohorts, using standard 3 + 3 dose-escalation design according to the modified Fibonacci rules (Tables 2 & 3, and Figure 1). The rules for determination of the MAD and MTD in the Fibonacci 3+3 design are described in Table 3.

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Once the MTD is reached, the Phase Ib part of the protocol will be initiated in patients with R/R PTCL or C-MYC positive DLBCL (Figure 2).

Duration of Treatment

Patients will be treated until one of the following events:

- Disease progression
- Unacceptable adverse event(s), DLTs
- Withdrawal of consent
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy.

Sample Size

Phase I

An estimated 9 patients (up to a maximum of 12) with R/R HL and NHL will be accrued to the Phase I study with 2 cohorts (Tables 2). A minimum of 3 patients will be treated in each dose cohort. If no DLT is reached in cohort 3, then a total of 6 patients will be treated at that dose level.

Phase Ib

The phase Ib part of the study will accrue a total of 15 patients.

Safety

Patients will be monitored carefully for the development of adverse events as well as clinical and/or radiographic evidence of disease response. Adverse events will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Efficacy Outcome

Overall response rates will be evaluated using clinical parameters, CT scan (PET scan is optional) and bone marrow biopsy, as outlined by the 2014 Lugano Classification[1].

Pharmacokinetic Analyses

- On day 1 of cycle 1 (Figure 3), blood samples will be obtained from patients predose (0h), 0.5, 2.5, and 4.5h after the start of infusion of carfilzomib. PK at 6.5h is optional. The purpose is to determine the plasma level of both carfilzomib and TGR-1202 (The start of infusion of carfilzomib is counted as 0h). The proposed time points are shown in Figure 3.

Table 1: **Regimen Description**

REGIMEN DESCRIPTION					
Agent	**Premedication Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Carfilzomib	IV hydration, dexamethasone	20-56** mg/m^2	IV over 30 minutes	Days 1, 8, 15	28 days
TGR-1202		600-800 mg	Oral	Once daily days 1-21	
** Doses as appropriate for assigned dose level with the following exception: on cycle 1 day 1 of all assigned dose level carfilzomib is dosed at 20 mg/m^2. Premedication for carfilzomib includes hydration with 250-500 ml of normal saline, and dexamethasone 4mg to prevent infusion reactions.					

Table 2: **Dose Escalation Scheme for the Combination of TGR-1202 and Carfilzomib**

Dose Escalation Schedule		
Dose Level	**Dose**	
	Carfilzomib (mg/m2) Given on days 1,8,15 of each 28-day cycle[(b)]	TGR-1202 (mg) Given once daily on days 1-21 of each 28-day cycle
Level -1[(a)]	20*/20	600
Level 1	20*/36	800
Level 2	20*/56	800

(a) In level -1, carfilzomib will be given at 20 mg/m2 on days 1, 8, 15 and TGR1202 on days 1-21.

(b) For cycle 1 day 1 of each cohort, carfilzomib will be given at 20 mg/m2. If the treatment is tolerated, the drug will be given at the assigned dose level for all other treatment days involving carfilzomib.

Table 3. Dose Escalation & De-Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 additional patients experience DLT, proceed to the next dose level. • If 1 or more of this group experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose (MAD), and the dose level below is the MTD.
$\geq$2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered).
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Figure 1. Drug Administration Schema

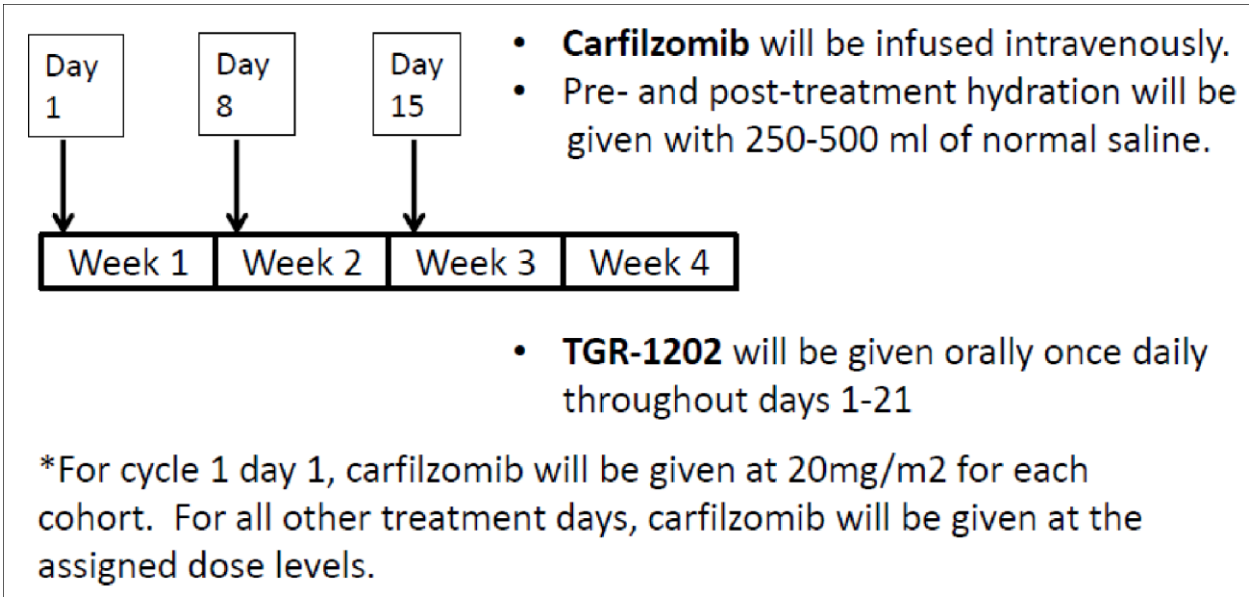
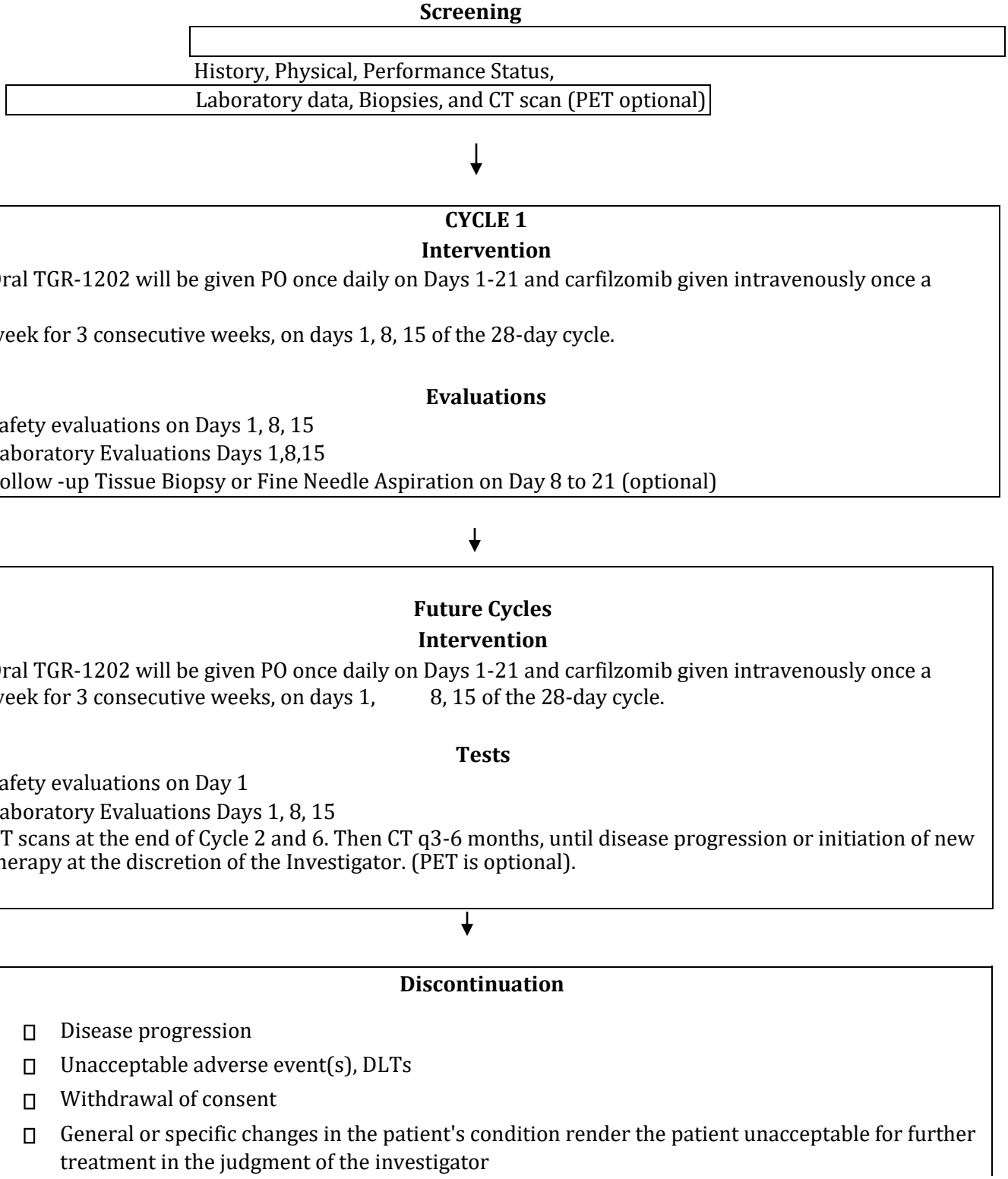


Figure 2: Study Plan Flow Chart Schema: Phase I



- An event that in the judgment of the treating physician warrant's discontinuation of therapy.

Figure 2: Study Plan Flow Chart Schema: Phase II

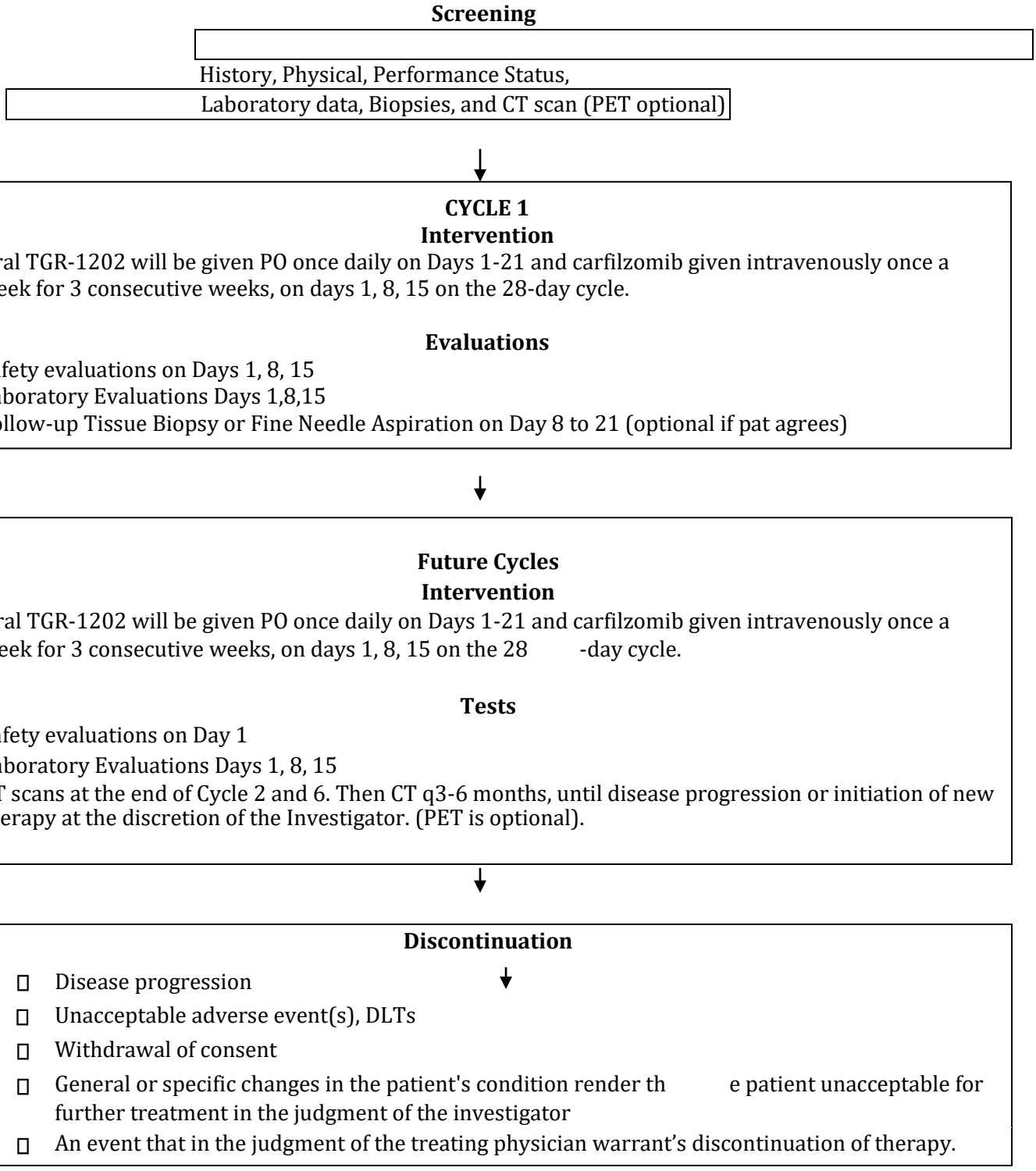
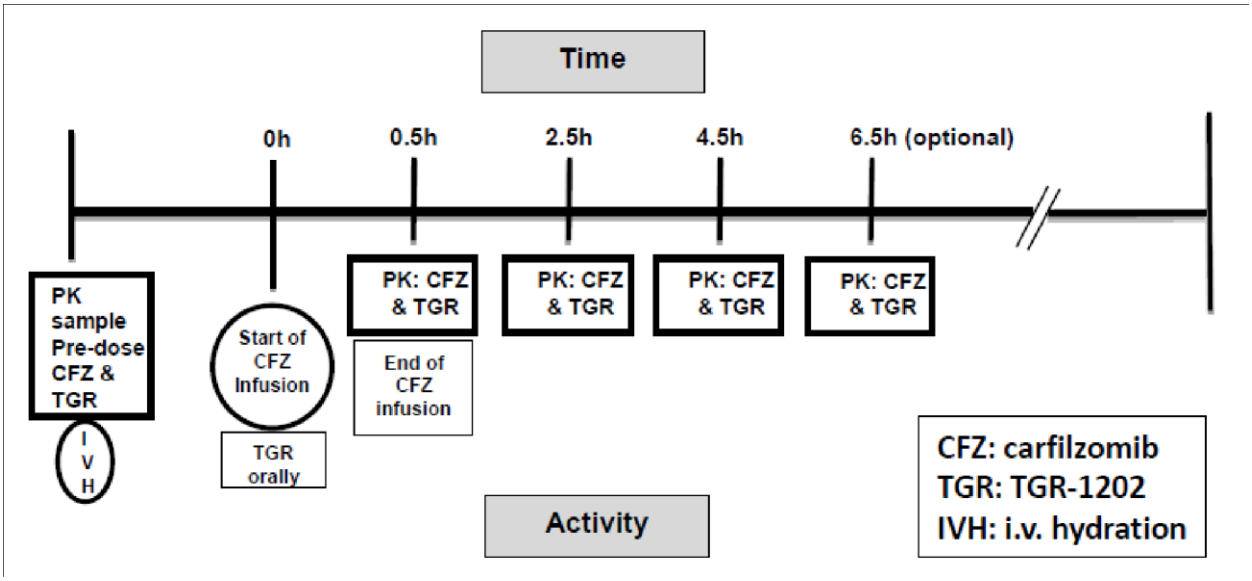


Figure 3. PK Studies on Cycle 1 Day 1



TITLE: Phase Ib Study of Carfilzomib and a PI3K Delta Inhibitor TGR-1202 in the Treatment of Patients with Relapsed or Refractory Lymphoma

1. OBJECTIVES

Phase I:

Primary Objectives

- Determine the maximum tolerated dose (MTD), maximally administered dose (MAD), and dose limiting toxicity (DLT) of the combination of TGR-1202 and carfilzomib.
- Evaluate the safety and toxicity of the combination of TGR-1202 and carfilzomib.

Secondary Objectives

- Describe the maximum number of cycles administered
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- Establish the pharmacokinetic profile for TGR-1202 and carfilzomib when given as a combination in Cycle 1.

Phase Ib:

Primary Objectives

- Evaluate the safety and toxicity of the combination of TGR-1202 and carfilzomib at the MTD dose level in patients with R/R PTCL and C-MYC positive DLBCL.

Secondary Objectives

- Estimate the ORR (complete + partial response) of the combination of TGR-1202 and carfilzomib in patients with R/R PTCL and C-MYC positive DLBCL.

- Estimate the DOR and PFS of the combination in patients with R/R PTCL and C-MYC positive DLBCL.

2. BACKGROUND

2.1 MALIGNANT LYMPHOMA

NHLs are a heterogeneous group of lymphoproliferative disorders originating in B-, T-, or natural killer (NK) lymphocytes. In the United States, B-cell lymphomas represent 80% to 85% of the cases, with 15% to 20% being T cell lymphomas; NK lymphomas are rare[2]. In 2010, an estimated 65,540 new cases of NHL were diagnosed and 20,210 patients died of the disease. NHL is the sixth leading site of new cancer diagnoses among men and women, accounting for 4% of new cancer cases and 4% of cancer-related deaths. As a group, the diffuse large-cell lymphomas (DLBCL) accounts for approximately one-third of all NHLs, and is the most common type of aggressive lymphoma. While the majority of patients with DLBCL can be cured with presently available combination immunochemotherapy, about 1/3 of these patients with DLBCL will eventually succumb to the lymphoma. Other types of aggressive lymphoma, for example, peripheral T cell lymphoma (PTCL), have inferior outcome to DLBCL, as the vast majority of PTCL develops resistance to chemotherapy and will relapse.

Dysregulated Myc is associated with resistance to chemotherapy and poor survival in patients with aggressive lymphomas such as “double hit” lymphoma, Burkitt lymphoma, transformed lymphoma and diffuse large B cell lymphoma (DLBCL) [3-8]. Novel strategies that targets this biology could markedly improve the outcome of these patients. To date no drugs that directly target Myc have been approved for the treatment of any malignancy. In fact, because Myc is involved in many essential functions in normal cells, direct c-Myc inhibitors could theoretically be associated with significant toxicity[9]. Alternatively, it may be advantageous to inhibit upstream cancer specific signals that converge on Myc as a therapeutic strategy to mitigate the poor risks associated with Myc dysregulation. Myc is known to form a positive feed-forward loop with the translation initiation factor eIF4F[10], which in turn is regulated by mTOR through the inhibitor 4EBP1[11]. PI3K is one of the most important upstream activators of mTOR[12], and recently the

ubiquitin-proteasome pathway was also reported to be involved in the activation of mTOR[13, 14]. Our hypothesis is that if the proteasome and PI3K pathways cooperate in the activation of mTOR, then combinations of drugs targeting these pathways will synergistically inhibit the mTOR-eIF4F-Myc axis and demonstrate potent activity in the treatment of Mycdependent aggressive lymphoma.

2.2 TGR-1202

2.2.1 PI3K AND PI3K-DELTA INHIBITORS

There are four mammalian isoforms of class 1 PI3Ks: PI3K-α, β,□ (class 1a PI3Ks) and PI3K-□ (a class 1b PI3K). These PI3Ks catalyze the production of phosphatidylinositol (3,4,5)trisphosphate (PIP3), leading to activation of the downstream effector pathways important for cellular survival, differentiation, and function. PI3K-α and PI3K-β are widely expressed, and are important mediators of signaling from cell surface receptors. PI3K-α is the isoform most often found mutated in cancers, has and is known to play a role in insulin signaling and glucose homeostasis[15, 16]. PI3K-β is activated in cancers where phosphatase and tensin homolog (PTEN) is deleted. Both isoforms are targets of small molecule therapeutics in development for cancer. PI3K-□ and P13K-□ are preferentially expressed in leukocytes, and are important in leukocyte function. PI3K-δ is activated by cellular receptors (e.g., receptor tyrosine kinases) through interaction with the SH2 domains of the PI3K regulatory subunit (p85), or through direct interaction with RAS. PI3K-γ is associated with G-protein coupled receptors (GPCRs), is responsible for the very rapid induction of PIP3 in response to GPCRs, and can be also activated by RAS downstream of other receptors. PIP3 produced by PI3K activates effector pathways downstream through interaction with pleckstrin homology (PH) domain containing enzymes (e.g., PDK-1 and AKT [PKB])[17].

In hematological malignancies including various histological types of lymphoma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and multiple myeloma (MM), overexpression and constitutive activation of PI3K-δ suggests that PI3K-δ inhibition could have

therapeutic benefit in these cancers[18-23]. The PI3K-δ isoform specific inhibitor CAL-101 (also known as GS-1101 and idelalisib) has demonstrated clinical activity in patients with hematologic malignancies. In heavily pre-treated patients with refractory CLL and bulky lymphadenopathy, single agent CAL-101 was highly active and clinically efficacious, providing a durable clinical benefit[24]. Moreover, inhibition of PI3K-δ not only affected cancer cells directly, but it also affected the ability of the cancer cells to interact with their microenvironment. Single agent treatment with CAL-101 has also been reported to be active in mantle cell lymphoma and refractory non-Hodgkin lymphoma, with some data suggesting that the antitumor efficacy may be mediated by pharmacological reduction of tumor-associated chemokines and cytokines[23, 25-29]. In refractory or relapsed indolent non-Hodgkin lymphoma (iNHL) and in CLL patients, CAL-101 has been combined with bendamustine and rituximab demonstrating robust clinical activity [30, 31]. Idelalisib was approved by the FDA in 2014 for the treatment of CLL and indolent lymphoma, but has not demonstrated activity in aggressive lymphoma. Although idelalisib is well tolerated for the majority of patients, more than one third patients experienced elevated transaminases, 11% of patients developed pneumonitis, and grade 3 or higher diarrhea or colitis occurred in 13% and 4% of the patients, respectively[32].

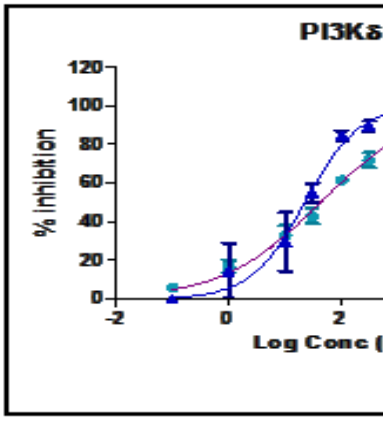
Interestingly, another PI3Kdelta inhibitor, TGR-1202, has a structure that is significantly different from idelalisib and is also found to have promising activity in indolent lymphoma[33]. Importantly, TGR-1202 is not associated with frequent transaminitis, pneumonitis, or colitis. The established roles of PI3K in cancer cells and in the biology of the tumor microenvironment support the development of PI3K-δ inhibitors. TGR-1202, due to its favorable toxicity profile, is an ideal candidate to combine with other targeting agents for the treatment of indolent and potentially aggressive lymphomas. For example, preliminary results by Deng et al. [34] have demonstrated that TGR-1202 is uniquely and potently synergistic with carfilzomib, a proteasome inhibitor (Section 2.4).

2.2.2 SUMMARY OF TGR-1202 PRECLINICAL EVALUATIONS

2.2.2.1 *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 Km value (100 μM). Selectivity over the other three isoforms, namely, α, β, and γ was also determined (Prasanna$_{abc}$ et al. 2011). 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 4).

Figure 4. TGR-1202 Potency against Human and Mouse PI3K Isoforms



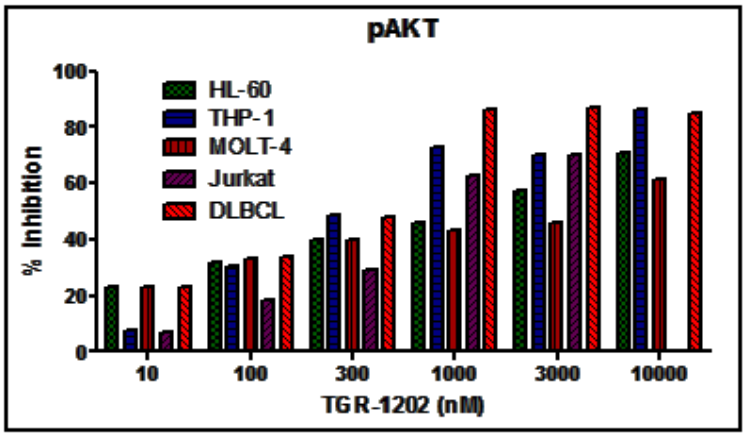
PI3K isoforms (Human)	IC_{50} (nM)
α	>10,000
β	1,116
γ	1,065
δ	22.23

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 (Seeta et al. 2012). 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 of B, T, and monocytic cell lines was achieved at a concentration between 0.5 -7.5 μM of TGR-1202.

Subsequent to cell viability, the effect of TGR-1202 on AKT phosphorylation (Seeta$_a$ et al. 2011, Seeta$_b$ et al. 2011, Seeta$_c$ et al. 2011, Seeta$_d$ et al. 2011, Seeta$_e$ et al. 2011) 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, demonstrating IC50 below 1.0 micromolar for 3 of the 5 studied cell lines (Figure 5).

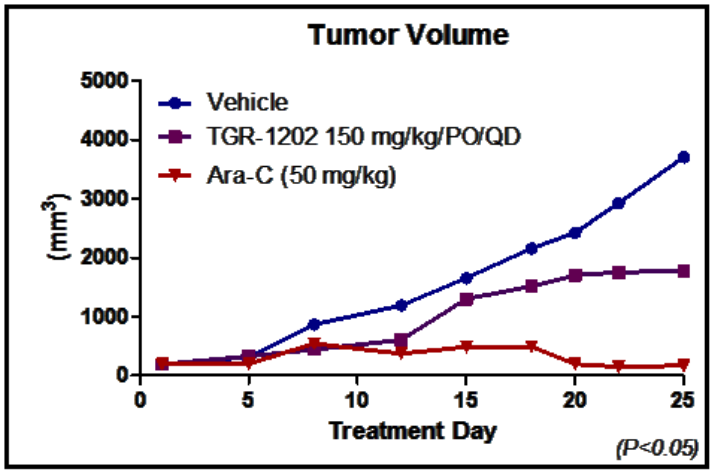
Figure 5. Reduction of pAKT by TGR-1202 in Cell Lines by Western Blotting



2.2.2.2 *IN VIVO* ACTIVITY

In vivo efficacy of TGR-1202 was confirmed in a subcutaneous mouse MOLT-4 xenograft model. Oral administration of 150 mg/kg/QD over a 25-day period resulted in a significant delay in tumor growth.

FIGURE 6. TGR-1202 IN VIVO EFFICACY



2.2.2.3 MECHANISM OF ACTION

TGR-1202 caused a dose-dependent inhibition of endogenous pAKT expression in all the cell lines tested with a half-maximal reduction observed at 300 nM concentration. Induction of apoptotic activity in cell lines was increased by ~50% across multiple cell lines representing NHL and CLL. These data support inhibition of the PI3K-AKT pathway as a major mechanism of action for TGR-1202.

2.2.3 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. TGR-1202 was administered orally. . No TGR-1202 related mortality occurred in the CD-1 mice population. Treatment related effects observed included slight decrease in leukocytes (0.5x relative control) and lymphocytes (0.5x relative to control) observed in both males and females at 750 mg/kg/day, increases in cholesterol (1.2x to 2.3x relative to control) noted in males and females at 150 and 750 mg/kg/day and increases in AST, ALT (2.2x to 2.6x relative to control), and GGT observed in the 750 mg/kg/day females. Organ weight changes in the liver (increased) and microscopic findings in the liver (centrilobular hypertrophy [males only], necrosis [males only], and bile duct hyperplasia and bile duct ectasia [females only]) were observed in mice dosed at 750 mg/kg/day RP-5264 (the free base of TGR-1202).

After a 14-day recovery period, there was complete recovery of the organ weight changes. There was complete recovery of the microscopic findings in the liver of females. There was incomplete recovery of the microscopic finding in the liver of male mice (centrilobular hypertrophy).

In conclusion, once daily oral administration of TGR-1202 was tolerated in mice at dose ranging from 50 and 150 mg/kg/day. The microscopic findings in the liver and the increases in serum cholesterol, and female only ALT, AST, and GGT levels at 750 mg/kg/day were considered adverse. The no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg/day.

TGR-1202 treatment-related clinical signs were observed in dogs dosed at 655/400 and 196.5/150 mg/kg/day. These were most severe in the first 9 days of the study in the 3 Group 4 females, which showed dehydration, diarrhea, vomitus, ocular discharge, and partial palprebal closure. Based on the severity of these findings, these 3 animals were euthanized on Day 9 and doses were reduced as tabulated above. Following reduction of the dose levels on
Day 9, treatment-related effects at doses of 400 mg/kg/day included diarrhea; soft, mucoid, abnormally colored stools; vomiting; ocular discharge; and partial palpebral closure. Isolated observations of thin appearance were also noted in dogs dosed at 655/400 mg/kg/day. There was an apparent gain in tolerance to TGR-1202 over the course of the study, as the instances of vomiting and diarrhea tended to decrease with time.

Test article-related decreases in body weight and food consumption, primarily limited to dogs of the 655/400 mg/kg/day group, were noted from the first week of the study. No other TGR-1202 treatment-related effects occurred on study. The thymus in the early termination animals and some of the Day 30 termination animals was noted at necropsy to be small. This observation was considered a secondary effect related to possible stress in the animals and not a direct effect of the test article.

The toxicokinetics of TGR-1202 in plasma was characterized in male and female beagle dogs when delivered by once daily oral capsule administration of TGR-1202 at dose levels of 65.5, 196.5, and 655 mg/kg from Day 1 to Day 8, and at dose levels of 50, 150 and 400 mg/kg from Day 9 to Day 28. Peak RP-5264 (free base of TGR-1202) concentrations occurred between 0.5 to 24 hours post-dose on Day 1, and between 1 and 10 hours post-dose on Day 28. Due to sustained concentrations, the terminal elimination phase was not reached. Exposure (mean C_{max} and $AUC_{[0-24]}$) were generally less than dose proportional between 65.5 and 655 mg/kg on Day 1 and between 50 and 400 mg/kg on Day 28. Exposure increased by up to 3.6-fold following repeated dosing for 28 days. There were no notable differences between male and female dogs.

In conclusion, 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).

Refer to the TGR-1202 Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

2.2.4 SUMMARY OF TGR-1202 CLINICAL EVALUATIONS

TGR-1202 is a highly specific and orally available PI3K delta inhibitor with nanomolar inhibitory potency. TGR-1202 is an isoflavone substituted pyrazolo pyrimidine. It is a p-Toluene sulphonic acid (p-TSA) salt of TGR-1202 base (TGR-1202 base is referred to as RP-5264). The specificity of TGR-1202 towards PI3Kδ is evidenced by >1000, 50 and 48-fold selectivity over α, β, and γ PI3K isoforms, respectively, in an enzyme based assay. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin and strongly implicated in various hematologic malignancies, and as a result, appears to be an ideal target to treat various lymphoid malignancies such as CLL and NHL, among others.

A multi-center (which includes the Center for Lymphoid Malignancy at Columbia University) Phase I dose-escalation clinical trial of TGR-1202 in patients with select hematologic malignancies is ongoing. TGR-1202 was well tolerated at doses up to 1800 mg daily given in the fasting state. No MTD was observed[35]. Subsequently the formulation was changed to a micronized one, given at the fed state. Again no MTD was observed at the cohort level of 1200mg daily[33]. The drug was well tolerated, without transaminitis and colitis, previously reported for idelalisib. TGR-1202 has demonstrated marked activity in patients with relapsed refractory CLL, with a 93% nodal response rate at doses ≥ 800 mg of initial formulation or any dose of micronized formulation. TGR-1202 appears to have promising activity in indolent lymphoma and mantle cell lymphoma. Although TGR-1202 has not demonstrated activity as single agent in aggressive lymphomas such as DLBCL, its excellent safety profile makes it an ideal candidate for rational combination with other drugs that targeting discrete biological signals that overlap with the PI3K pathway, for example, proteasome inhibitors[34], as discussed in Section 2.4.

2.3 CARFILZOMIB

2.3.1 PROTEASOME AND PROTEASOME INHIBITOR

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity. The ubiquitin-proteasome pathway is the major quality-control pathway for newly synthesized proteins[36]. Furthermore, through targeted destruction of regulatory proteins, e.g. cyclins and cyclin-dependent kinase inhibitors[37], the proteasome regulates numerous cellular functions that are important for the proliferation and survival of cancer cells.
Consistent with these findings, proteasome inhibitors are found to induce death and prevent proliferation of cancer cells[38, 39].

Bortezomib is a first-in-class proteasome inhibitor approved for clinical use. O'Connor et al. reported the clinical activity of bortezomib in the treatment of indolent Non-Hodgkin lymphoma (NHL) and mantle cell lymphoma (MCL), leading to its approval by the FDA for relapsed and refractory MCL[40]. Bortezomib has also demonstrated clinical activities in a number of other hematological malignancies as a single agent or in combinations[41]. As a single agent, however, bortezomib has not demonstrated promising activity in aggressive lymphoma. Since Wilson et al. first reported inclusion of bortezomib with EPOCH-R[42], bortezomib has been combined with CHOP and other regimens[43]. These studies demonstrate the feasibility of combining bortezomib with chemotherapeutic agents, and in some cases produce benefit in select subtypes of lymphoma. However, bortezomib is associated with significant peripheral neuropathy, a dose-limiting toxicity (DLT) that may limit its dosage and utility as part of combination chemotherapy regimens. A promising strategy is to combine proteasome inhibitors and novel biologic agents to synergistically target oncogenic pathways.

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsinlike active site of the 20S proteasome[44]. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib. A Phase 1 study conducted by O'Connor et al has demonstrated that carfilzomib is safe, and produces essentially none of the neuropathy seen with

bortezomib[45]. Preliminary results from by Deng et al. have demonstrated that carfilzomib is highly synergistic with TGR-1202, a PI3Kdelta inhibitor[34].

2.3.2 TOXICOLOGY STUDIES OF CARFILZOMIB

A chronic toxicity study in rats was preceded by a GLP-compliant, 28-day, repeat-dose study in which carfilzomib was administered for 2 complete cycles of once daily for 5 days followed by 9 days of rest. In this study, the STD10 was determined to be 2 mg/kg (12 mg/m2) based upon mortality of 5% of the animals at this dose and > 10% at the next highest dose (24 mg/m2).
Similar target organ toxicities were seen in the 28-day repeated toxicity study as is noted below in the 6-month chronic rat study. In a 6-month, GLP-compliant study, carfilzomib was administered to 25 animals/sex/group at doses of 6, 12, and 24 mg/m2 (1, 2, and 4 mg/kg) for 6 complete 28-day cycles of once daily dosing for 2 days repeated weekly for 3 weeks followed by 12 days of rest. Toxicokinetics and PDn were assessed in satellite cohorts. Mortality of 30% of the animals was noted at 24 mg/m2 and in 6% of animals at 12 mg/m2. The causes of death for these animals, when they could be determined, were gastric hemorrhage/necrosis, cardiac failure, and renal tubular failure (associated with vascular thrombi). Toxicities observed in animals in the high-dose group sacrificed at the end of the study included thrombocytopenia, decreased RBC counts with a concomitant increase in reticulocytes, induction of an acute phase response (increased fibrinogen and circulating neutrophils and monocytes), azotemia (increased BUN) associated with an increased rate of chronic progressive nephropathy (common to this strain of rat), hepatocellular hypertrophy and periportal fatty vacuolation in the liver that was not associated with altered liver enzyme levels, and decreased cellularity in the thymus and spleen. In the remaining animals at 12 mg/m2 (2 mg/kg), thrombocytopenia, increased reticulocytes, and signs of an acute phase response were observed. Proteasome inhibition measured in whole blood 1 hour after the first dose was > 90% for all dose levels in this study. The STD10 was determined to be 12 mg/m2 (2 mg/kg) based upon rate of mortality in the high-dose group.

A chronic toxicity study in monkeys was preceded by a GLP-compliant, 28-day, repeat dose study in which carfilzomib was administered for 2 complete cycles of once daily for 5 days followed by 9 days of rest. In this study, the highest non-severely toxic dose (HNSTD) was determined to be 12 mg/m2 (1 mg/kg) based upon mortality in animals at the next highest dose (24 mg/m2). Similar

target organ toxicities were seen in the 28-day repeated toxicity study, as is noted below in the 9-month chronic study. In this study, carfilzomib was administered to cynomolgus monkeys (4–6 per sex per dose) at doses of 6, 12, and 24 mg/m2 (0.5, 1, and 2 mg/kg) for 9 complete cycles, once daily for 2 days repeated weekly for 3 weeks followed by 12 days of rest. At 24 mg/m2, there was an unscheduled death of 1 male in Cycle 6 due to multiorgan toxicities, including cardiac inflammation, pulmonary inflammation and edema, and renal dysfunction, and an early sacrifice of 1 female in Cycle 5 due to declining physical condition associated with severe nonregenerative anemia and hypoalbuminemia. At doses of 12 and 24 mg/m2, decreases in RBCs along with reduced hemoglobin levels and hematocrit with increased reticulocytes were noted on Day 17 of each cycle (24 hours after the last dose), but recovered during the 12-day nondosing periods of each cycle. Also noted at these dose levels were induction of an acute phase response (increased fibrinogen, neutrophils, and monocytes and decreased albumin) and azotemia (increased BUN and serum creatinine) associated with proteinuria, hematuria, and increased kidney weight. The azotemia was associated with interstitial inflammation, altered tubule size, and glomerulopathy in the kidney. Inflammation was also noted in the heart and interstitial regions of the lung at these dose levels. The HNSTD in this study was determined to be 6 mg/m2 (0.5 mg/kg) based upon mortality at the high dose (24 mg/m2), histomorphologic changes in the kidney, proteinuria, and hematuria at 12 mg/m2. Proteasome inhibition, measured in whole blood 1 hour after the first dose, was > 90% for all dose levels in this study.

2.3.3 CYTOCHROME P450

In an in vitro study using human liver microsomes, carfilzomib showed modest direct and timedependent inhibitory effect on human cytochrome P450 3A4/5 (CYP3A4/5). In vitro studies indicated that carfilzomib did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. A clinical trial of 17 patients using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetic profile of midazolam was unaffected by concomitant carfilzomib administration. Carfilzomib is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates.

2.3.4 PRECLINICAL ANTITUMOR ACTIVITY OF CARFILZOMIB

Incubation of tumor-derived cell lines in culture for 1 hour with carfilzomib leads to rapid inhibition of proteasome activity, followed by accumulation of polyubiquitinated proteins and induction of apoptosis[44]. This brief exposure time, which mimics in vivo exposure, induces cell death in both hematological and solid tumor cell lines. Hematological tumor cell lines, particularly multiple myeloma, are the most sensitive to such carfilzomib treatments, with IC50 values ranging from 31 to 164 nM. Continuous (72-hour) exposure to carfilzomib is associated with more potent antitumor activity across a broad panel of tumor cells (IC50 values ranging from 2.4 to 20 nM). Thus, intensive dosing with carfilzomib was examined initially in animal efficacy and toxicity studies and subsequently in clinical studies. Intensive dosing strategies involved administration of a second dose of carfilzomib within a 24-hour period in order to delay the recovery of proteasome function within target cells. Sustained proteasome inhibition for 60 to 72 hours achieved with a second dose of carfilzomib given on Day 2 lead to significant antitumor activity in animal models that are resistant to bortezomib given on its clinical schedule (Day 1 and Day 4)[44].

The antitumor efficacy of carfilzomib has been evaluated in immunocompromised mice implanted with a variety of human tumor cell lines, including HT-29, a human colorectal adenocarcinoma cell line[44]. A statistically significant reduction from baseline in tumor size was seen when carfilzomib was administered on a weekly schedule of Day 1/Day 2[44].

2.3.5 PHASE 1 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY

O'Connor et al. conducted the first phase I trial evaluating the safety and efficacy of carfilzomib in relapsed or refractory hematologic malignancies[45]. Eight dose groups of three to six patients received 5 consecutive days of carfilzomib intravenously at doses of 1.2, 2.4, 4, 6, 8.4, 11, 15, and 20 mg/m^2 within 14-day cycles. At 20 mg/m^2, grade 3 febrile neutropenia and grade 4 thrombocytopenia were reported, establishing 15 mg/m^2 as the maximum tolerated dose (MTD). No grade 3 or 4 peripheral neuropathies were reported. Antitumor activity was observed at doses equal to or higher than 11 mg/m^2: one unconfirmed complete response, one partial response, and two minimal responses.

A separate phase I clinical trial, PX-171-002, tested carfilzomib in subjects with relapsed/refractory hematologic malignancies[46]. During the dose escalation portion of the trial, 37 subjects received carfilzomib on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Subjects with multiple myeloma (MM), non-Hodgkin's Lymphoma (NHL), Waldenström's macroglobulinemia, and Hodgkin's lymphoma (HL) were enrolled on the study. No DLTs were observed in the initial seven cohorts (doses ranged from 1.2 to 15 mg/m^2) of three subjects each. At the 20 mg/m^2 dose level, one of eight patients experienced a Grade 3 renal failure at
Cycle 1, Day 2 which was considered possibly related to study drug and lasted for six days.
The patient continued on study for the remainder of Cycle 1 before having disease progression. At the 27 mg/m^2 dose level, one of six subjects experienced a DLT during Cycle 1, consisting of severe hypoxia with pulmonary infiltrates following Day 2 of dosing. In subjects where the 27 mg/m^2 dose was efficacious, a "first dose effect" was seen that included a constellation of findings that appeared to be the clinical sequelae of rapid tumor lysis syndrome (TLS) and/or cytokine release. This syndrome was notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion. On the second day, three of five subjects with multiple myeloma experienced an increase in creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all three subjects were re-challenged with carfilzomib without recurrence of the events. Interestingly, all three subjects had a rapid decline in serum and/or urine M-protein levels; two subjects achieved a PR and the third subject achieved a minimal response (MR). There were no consistent changes in potassium, calcium, phosphorous, or uric acid levels although some increases in LDH and other markers of tumor lysis were noted. Because of the possible TLS and reversible creatinine elevations, hydration and very-low dose dexamethasone prophylaxis were instituted in subsequent studies and have essentially eliminated clinically significant TLS/creatinine elevations and the other "first-dose" effects. Hematologic toxicities were primarily mild or moderate. The thrombocytopenia reported with carfilzomib is cyclical and similar to that reported with bortezomib. The cause and kinetics of the thrombocytopenia following treatment are different from those of standard cytotoxic agents. In general, it is recommended that in order to maximize the benefit of carfilzomib, subjects with thrombocytopenia should be supported as clinically indicated rather than having treatment reduced due to thrombocytopenia.

Of the 37 evaluable patients enrolled in the dose escalation phase of PX-171-002, 20 had MM. Four MM patients achieved a partial response (PR), one of two at the 15 mg/m^2 dose, one of six

at the 20 mg/m^2 dose, and two of five at the 27 mg/m^2 dose. The responses have been rapid in onset, beginning in some subjects after 1-2 doses. The duration of response (DOR) ranged from 134 to 392 days. The minimal effective dose was 15 mg/m^2 wherein >80% proteasome inhibition in peripheral blood and mononuclear cells was observed one hour after dosing. The median number of prior therapies for subjects on this trial was five, and responses were seen in subjects who had relapsed from (including some refractory to) bortezomib and/or immunomodulatory agents. Stable disease also noted in four NHL and five MM subjects, with subjects on therapy for up to 409 days. Such prolonged therapy, at "full" twice-weekly doses, is not possible with bortezomib. These results led to the initiation of two Phase 2 studies.

An ongoing phase I study investigated weekly carfilzomib in combination with dexamethasone for patients with relapsed or refractory MM. Preliminary results of 18 patients have been reported in the abstract form[47]. The 45 and 56 mg/m^2 dosing cohorts enrolled 3 patients each, and the 70 and 88 mg/m^2 dosing cohorts enrolled 6 patients each. Patients have received a median of 5.5 cycles of treatment. At 88 mg/m^2, 2 dose-limiting toxicities (DLTs) were observed: grade [Gr] 3 dyspnea and Gr 3 vomiting. All 18 patients were evaluable for safety. The only grade 3 adverse event (AE) reported in more than 1 patient was increased blood creatinine (n=2). Four serious AEs were reported in 3 patients: Gr 3 dyspnea, Gr 3 pneumonia, Gr 3 increased blood creatinine, and Gr 4 hyponatremia. No peripheral neuropathy was reported. Six patients discontinued treatment for the following reasons: AEs of decreased renal function (n=1) and dyspnea (n=1), progressive disease (n=2), physician decision (n=1), and withdrawal of consent (n=1). Five patients required a dose reduction from 88 mg/m2 to 70 mg/m2 (1 due to an AE, 1 due to a DLT, and 3 per protocol due to the 2 DLTs in the 88 mg/kg2 cohort); 2 of the 5 patients had an additional dose reduction owing to AEs. PK analysis (n=12) from patients who received 20, 70, or 88 mg/m2 of carfilzomib showed a dose-dependent increase in mean Cmax (703, 2640, and 3172 ng/mL, respectively) and AUC (283, 1045, and 1247 h·ng/mL, respectively) for carfilzomib. The mean terminal half-life was ~0.8 h. Fifteen patients were included in the response evaluation; 3 patients did not have a postbaseline assessment at the time of the data cutoff. The ORR was 67%, and the CBR was 87% (4 patients achieved a complete response, 1 very good PR, 5 PR, and 3 MR). One patient had stable disease, and 1 patient was not evaluable for response, as the patient had a DLT and was no longer on treatment. Median time to response for patients that achieved a ≥PR (n=10) was 1.6 months.

2.3.6 PHASE 2 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY

Unfortunately to date, there has been very little phase 2 experience with carfilzomib in patients with lymphoma. However, there is abundant data in patients with myeloma that is informative for the proposed study. Two Phase 2 clinical studies have been completed with carfilzomib in MM patients, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39 in Part 1, N=120 in Part 2) in relapsed MM[48, 49]. In both studies, patients were dosed with 20 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 on a 28 day schedule. In these studies there were four cases of suspected or documented TLS prior to institution of the prophylaxis guidelines. Since these guidelines were implemented, no further cases of TLS have been reported including in >350 additional patients with relapsed or refractory MM treated in ongoing Phase II studies. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increased in serum creatinine that were primarily < Grade 2 and were transient, rapidly reversible, and non-cumulative. A very low rate of treatment-emergent peripheral neuropathy, 2.2% Grade 3/4, was observed in PX-171-003-A0 despite the fact that 78% of patients had Grade 1/2 neuropathy upon study entry. The response rate in PX-171-003A0 was 18% PR, 7% MR and 41% SD in these patients that entered the study with progressive disease and were refractory to their most recent therapy, often including bortezomib and/or an immunomodulatory drug (usually lenalidomide). The median time to progression on the PX171-003-A0 study was 5.1 months with a DOR of 7.4 months (mean follow up of 7.6 months).

A “stepped up” dosing schedule, referred to as 20/27 mg/m^2 has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) in order to maximize the clinical benefit of carfilzomib[50]. Patients receive 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter. The study completed enrollment of 266 patients. To date, this stepped up dosing schedule has been well tolerated. An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 patients to be enrolled on the 20/27 schedule and agreed that the trial should proceed without modification. No cases of TLS were observed and rates of BUN and creatinine elevation dropped sharply, with Grade 3/4 renal impairment dropping to 2.2% in A1(from 15% in A0), most

likely due to hydration and very low dose dexamethasone. The other most common adverse events were similar to the A0 portion of the study. Treatment-emergent peripheral neuropathy remains low the study with 15% Grade 1/2 and one (0.7%) Grade 3/4 event reported to date on PX-171-003-A1. In addition, anemia in the PX-171-003-A1 (higher dose) were lower than those reported in the PX-171-003–A0 portion of the study, possibly indicating that the higher dose of carfilzomib is achieving better clearing of neoplastic cells in the bone marrow allowing superior normal marrow reconstitution. Rates of thrombocytopenia and neutropenia were similar in the two cohorts, with Grade 3 neutropenia in ~5% without any Grade 4 neutropenia to date.

In PX-171-004[49], 129 bortezomib-naive patients with R/R MM (median of 2 prior therapies) were separated into Cohort 1, scheduled to receive intravenous carfilzomib 20 mg/m(2) for all treatment cycles, and Cohort 2, scheduled to receive 20 mg/m(2) for cycle 1 and then 27 mg/m(2) for all subsequent cycles. The primary end point was an overall response rate (>/= partial response) of 42.4% in Cohort 1 and 52.2% in Cohort 2. The clinical benefit response
(overall response rate + minimal response) was 59.3% and 64.2% in Cohorts 1 and 2, respectively. Median duration of response was 13.1 months and not reached, and median time to progression was 8.3 months and not reached, respectively. The most common treatmentemergent adverse events were fatigue (62.0%) and nausea (48.8%). Single-agent carfilzomib elicited a low incidence of peripheral neuropathy-17.1% overall (1 grade 3; no grade 4)-in these pretreated bortezomib-naive patients. Thus, carfilzomib can induce very high levels of response in patients who have not previously been treated with bortezomib and, even in bortezomibtreated patients, substantial anti-tumor activity is observed. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients on these studies have been treated for >12 cycles with good tolerability and no cumulative toxicity (e.g., bone marrow, severe fatigue, or neuropathy) have not been observed. These data formed the basis of FDA approval of carfilzomib for the treatment of relapsed and refractory MM, and the approved dosing schedules are 20mg/m^2 for cycle 1, and 27 mg/m^2 in subsequent cycles if tolerated. The drug is given as an intravenous infusion over 2-10 minutes.

Higher dose of carfilzomib as a monotherapy has been used in a small cohort of 47 patients with solid tumor or lymphoma. In these patients carfilzomib was given intravenously over a longer duration, 30 minutes, at the dose of 20 mg/m^2 on Cycle 1 Days 1 and 2 only, followed by increased doses (36, 45, 56, 70, or 88 mg/m^2) for the remainder of treatment. No DLTs were seen in the

initial 20/36 mg/m^2, 20/45 mg/m^2, or 20/56 mg/m^2 dose cohorts. Reversible DLTs were recorded in 2 patients in the 20/70 mg/m^2 cohort: 1 patient experienced Grade 3, probably treatment-related proteinuria and 1 patient experienced Grade 3, possibly treatment-related renal tubular necrosis and Grade 4 thrombocytopenia lasting 28 days; both patients were successfully re-challenged and continued on treatment at reduced doses. The MTD was therefore determined to be 56 mg/m^2.

2.3.7 PHARMACODYNAMICS OF CARFILZOMIB

Proteasome subunit activities in blood and PBMC samples from Phase 1b/2 Studies PX-171005, PX-171-006, and PX-171-007 were measured before and after treatment with carfilzomib. Intravenous administration of carfilzomib over 2 to 10 minutes results in suppression of proteasome CT-L activity when measured in blood 1 hour after the first dose. Inhibition of proteasome CT-L activity was comparable in whole blood and PBMCs. On Day 1 of Cycle 1, CT-L inhibition in PBMCs ranged from 79% to 89% at 15 mg/m2 and from 82% to 83% at 20 mg/m2. Inhibition of the latent membrane protein 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the immunoproteasome ranged from 26% to 32% and 41% to 49% at 20 mg/m2, while little to no inhibition of the Beta1 or Beta2 was observed. On Day 1 of Cycle 2, CT-L inhibition in PBMCs following a dose of 27 mg/m2 was 76% to 92%.

Proteasome inhibition was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing, with 30-minute and bolus infusions. Near-complete recovery of proteasome activity was observed in PBMCs between cycles, that is, after 12 days without treatment. Upon IV administration of 20 mg/m2 carfilzomib over 30 minutes, the level of proteasome inhibition was similar to that observed in subjects receiving a 2- to 10-minute infusion. At 20 mg/m2, inhibition of CT-L activity in blood and PBMC was 69.1% and 85.0%, respectively, and inhibition of LMP2 and MECL1 in PBMC was 30.2% and 50.3%, respectively. At the carfilzomib dose of 36 mg/m2 inhibition of CT-L activity in blood and PBMC was 73.5% and 86.9%, respectively, and inhibition of LMP2 and MECL1 in PBMC was 33.6% and 54.3%, respectively. At 45 mg/m2, inhibition of CT-L activity in blood and PBMC was 89.3% and 94.1%, respectively, and inhibition of LMP2 and MECL1 in PBMC was 53.8% and 77.5%, respectively.

2.3.8 PHARMACOKINETIC PROFILE OF CARFILZOMIB

Intensive PK sampling with single- and multiple-dose PK characterization was evaluated in Studies PX-171-005 and PX-171-007. Similar to the results from rodents and monkeys, carfilzomib demonstrated rapid clearance from plasma following IV administration to human subjects. Pharmacokinetic parameter calculations could not be performed for doses < 11 mg/m2, due to a large number (> 50%) of samples with concentration values below the limit of detection or high intra- and intersubject variability. At doses ≥ 15 mg/m2, systemic clearance values on Cycle 1 Day 1 ranged from 151 to 263 L/h, exceeding liver blood flow, and terminal t1/2 values were between 0.4 to 1.2 hours. The Cmax and AUC following a single IV dose of 27 mg/m2 over 2 to 10 minutes was 4232 ng/mL and 379 ng•hr/mL, respectively. While definitive dose proportionality cannot be concluded due to the small number of observations available for analysis, a dose-dependent increase in total exposure (AUC) and Cmax was seen between 20 and 56 mg/m2. Following repeated doses of carfilzomib at 15 and 20 mg/m2, the AUC and t1/2 were similar on Days 1 and 15 or 16 of Cycle 1, suggesting no systemic carfilzomib accumulation.

2.3.9 ABSORPTION OF CARFILZOMIB

Carfilzomib is administered intravenously (IV) ; therefore, absorption is not applicable.

2.3.10 DISTRIBUTION OF CARFILZOMIB

The mean volume of distribution at steady state (VSS) after a 20 mg/m2 dose of carfilzomib was 28 L in subjects with multiple myeloma. In an in vitro study, binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4.0 micromolar and this extent of binding was not concentration dependent. Similarly, plasma protein binding of carfilzomib in multiple myeloma subjects with normal renal function and subjects with mild to severe renal dysfunction ranged from 97.6% to 98.3% (Study PX-171-005).

2.3.11 METABOLISM OF CARFILZOMIB

Upon administration, carfilzomib was rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated in vitro by human hepatocytes, were peptide fragments (M14, M15) and the diol of carfilzomib (M16), suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. These metabolites were likely systemically formed, because a study with rat blood and tissue (kidney, heart, lung, and liver) homogenates demonstrated rapid formation of these metabolites. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. Each of the metabolites (M14, M15, and M16) lacks an epoxyketone pharmacophore and has no known biologic activity. In addition, the metabolites in humans are formed in preclinical species and there are no unique and disproportionate metabolites in humans.

2.3.12 EXCRETION OF CARFILZOMIB

Renal and biliary elimination of unlabeled carfilzomib was evaluated in subjects with multiple myeloma or solid tumors in lieu of a radiolabeled mass balance study in healthy volunteers. The excretion profile of carfilzomib and predominant metabolites was assessed by a 24-hour collection of urine and fecal samples in Study PX-171-008 and urine sample collection in Study PX-171-005. The metabolites of carfilzomib are primarily eliminated by the kidneys. Within 24 hours following administration of a single 27 mg/m2 IV dose of carfilzomib to subjects with multiple myeloma or solid tumors, approximately 30% of the administered dose of carfilzomib was excreted in urine as metabolites M14 (approximately 24%–31%) and M15 (approximately 2%). Urinary excretion of parent compound was negligible (0.3% of the total dose). These results suggest that carfilzomib is primarily metabolized to M14 before being excreted in urine. A small amount of metabolite M14 (0.2%) was recovered in feces with no detection of carfilzomib and metabolite (M15 and M16) in fecal samples. The relatively low recovery observed in urine and fecal samples could be due to the collection time limited to 24-hour and measurements not accounting for minor

metabolites. In addition, carfilzomib is peptidic in nature and irreversibly binds to its target; drug recovery would be expected to be limited by target binding in cells that are slow to turnover proteasomes and amino acids (leucine and phenylalanine) that may be incorporated into normal biosynthetic pathways.

2.4 RATIONALE FOR THE STUDY

Dysregulated Myc is associated with resistance to chemotherapy and poor survival in patients with aggressive lymphomas[3-6]. Novel strategies that target this biology could markedly improve the outcome of these patients. To date no drugs that directly target Myc have been approved for cancer treatment. In fact, since Myc is involved in many essential functions in normal cells, direct Myc inhibitors may theoretically be associated with significant toxicity. Alternatively, it may be advantageous to inhibit upstream cancer specific signals that converge on Myc as a therapeutic strategy to mitigate the poor risks associated with Myc dysregulation.

Myc is known to form a positive feed-forward loop with the translation initiation factor eIF4F[10], which in turn is regulated by mTOR through the inhibitor 4EBP1[11]. PI3K is one of the most important upstream activators of mTOR[12], and recently the ubiquitin-proteasome pathway was also reported to be involved in the activation of mTOR[13, 14]. Our hypothesis is that if the proteasome and PI3K cooperate in the activation of mTOR, then combinations of drugs targeting these pathways will synergistically inhibit the mTOR-eIF4F-Myc axis and demonstrate potent activity in the treatment of Myc-dependent aggressive lymphoma. Results from our laboratory have demonstrated that carfilzomib and a PI3K-delta inhibitor, TGR-1202, are highly synergistic in models of aggressive B- and T-cell lymphoma, through downregulation of c-Myc.

Preliminary results: We surveyed interactions between 2 PI3K-delta inhibitors (idelalisib/CAL101 and TGR-1202) and 2 proteasome inhibitors (bortezomib and carfilzomib) using high throughput screening (HTS). We chose these drugs based on their safety in patients. Further, 3 of these 4 drugs are FDA approved, idelalisib for indolent lymphoma, bortezomib for multiple myeloma (MM) and mantle cell lymphoma (MCL), and carfilzomib for MM. The combination TGR-1202 + carfilzomib caused more synergism in growth inhibition (Figure 7A) and apoptosis than the

combinations TGR-1202 + bortezomib, Cal-101 + carfilzomib, and Cal-101 + bortezomib in models of diffuse large B cell lymphoma (DLBCL). Figure 7B demonstrated both TGR-1202 + carfilzomib and Cal-101 + bortezomib were more effective than the single agents in the inhibition of AKT and Raptor. In contrast, TGR-1202 + carfilzomib was markedly more potent than Cal-101 + bortezomib and the single agents on the inhibition of phosphorylated 4EBP1, eIF4F subunits (A/E/G), and c-Myc in DLBCL. The same results were observed in T-cell acute lymphoblastic leukemia (T-ALL) and MCL, supporting combining PI3K and proteasome inhibitors as a therapeutic strategy in Myc dependent aggressive lymphoma. The combination of TGR-1202 and carfilzomib is particularly synergistic, therefore promising for clinical studies.

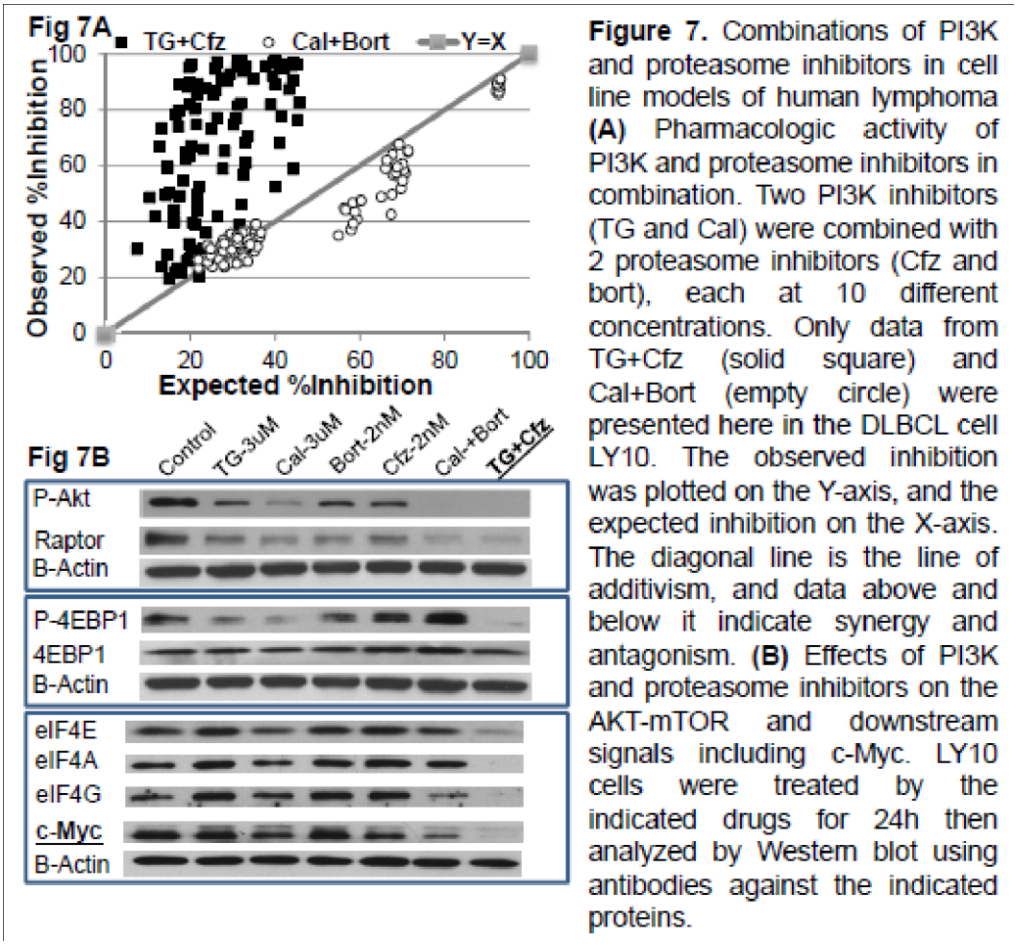


Figure 7. Combinations of PI3K and proteasome inhibitors in cell line models of human lymphoma **(A)** Pharmacologic activity of PI3K and proteasome inhibitors in combination. Two PI3K inhibitors (TG and Cal) were combined with 2 proteasome inhibitors (Cfz and bort), each at 10 different concentrations. Only data from TG+Cfz (solid square) and Cal+Bort (empty circle) were presented here in the DLBCL cell LY10. The observed inhibition was plotted on the Y-axis, and the expected inhibition on the X-axis. The diagonal line is the line of additivism, and data above and below it indicate synergy and antagonism. **(B)** Effects of PI3K and proteasome inhibitors on the AKT-mTOR and downstream signals including c-Myc. LY10 cells were treated by the indicated drugs for 24h then analyzed by Western blot using antibodies against the indicated proteins.

3. PATIENT SELECTION

3.1 INCLUSION CRITERIA FOR LYMPHOMA

- Phase I: Patients with relapsed or refractory Hodgkin lymphoma or non-Hodgkin lymphoma. Patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are also eligible. In addition, patients with NHL other than diffuse large B cell lymphomas (DLBCL) must have received at least 2 prior therapies. Patients with DLBCL and HL will be eligible if there is no available standard therapy.

- Phase Ib: Patients must have histologically confirmed R/R PTCL or C-MYC positive DLBCL (as defined by WHO criteria and IHC staining of C-MYC). The patients with PTCL or DLBCL will be eligible if there is no available standard therapy.
- Must have received front-line chemotherapy. No upper limit for the number of prior therapies. Patients may have relapsed after prior autologous stem cell transplant or allogeneic stem cell transplant.
- Evaluable Disease in the Phase I, and measurable disease for the phase Ib study as defined in Section 11 in the Phase II.

- Age ≥18 years

- ECOG performance status ≤ 2
- Patients must have adequate organ and marrow function as defined below:
  - absolute neutrophil count ≥1,000/dL
  - platelets ≥75,000
  - total bilirubin ≤1.5X institutional limits

    Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN; aPTT, PT not to exceed 1.2 × ULN
  - AST(SGOT)/ALT(SGPT) ≤2.0X institutional upper limit of normal ○ Serum creatinine within normal institutional limits
    - OR
  - Measured creatinine clearance ≥50 mL/min/for patients with creatinine levels above institutional normal.
  - Left ventricular ejection fraction (LVEF) ≥50% as defined by ECHO or MUGA.

- Negative urine or serum pregnancy test for females of childbearing potential. All females of childbearing potential must use an effective barrier method of contraception (either an IUD or double barrier method using condoms or a diaphragm plus spermicide) during the treatment period and for at least 1 month thereafter. Male subjects should use a barrier method of contraception during the treatment period and for at least 3 months thereafter.
- Ability to understand and the willingness to sign a written informed consent document.

3.2 EXCLUSION CRITERIA

- Prior Therapy
    - Exposure to chemotherapy or radiotherapy within 2 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.
    - Systemic steroids that have not been stabilized (≥ 5 days) to the equivalent of ≤10 mg/day prednisone prior to the start of the study drugs. ○

    No other concurrent investigational agents are allowed.
- Central nervous system metastases, including lymphomatous meningitis will be allowed in the phase II study, but will not be allowed in the phase I.
- History of allergic reactions to TGR-1202 or carfilzomib.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant women
- Nursing women
- Active concurrent malignancy (except non-melanoma skin cancer, carcinoma in situ of the cervix, low risk prostate cancer). If there is a history of prior malignancy, the patient must be disease-free for ≥ 2 years.
- Patients with a low grade lymphoma or CLL and a concurrent high grade lymphoma transformed from the low grade lymphoma or CLL will be eligible.
- Patients known to be Human Immunodeficiency Virus (HIV)-positive
- Patients with active hepatitis A, hepatitis B, or hepatitis C infection

- Concomitant use of CYP3A4 inhibitors (see Appendix 2) Significant cardiac abnormalities such as:
    - Myocardial infarction within 6 months of C1D1;
    - An ECG recorded at screening showing evidence of cardiac ischemia (ST depression of ≥2 mm, measured from isoelectric line to the ST segment). If in any doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present;
    - Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix 4) and/or ejection fraction <50% by MUGA and ECHO;
- A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter-defibrillator (AICD).

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

Eligible patients will be enrolled on study by the study team.

Following enrollment, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled.

4.2 SCREENING

All potential study patients will be screened and eligibility determined prior to enrollment. Unless otherwise specified, the following procedures and evaluations will be performed as noted in the study calendar (Section 10) prior to the start of study drugs (cycle 1, dose 1):

- Obtain written informed consent and privacy authorization prior to initiating any protocolrequired procedure that is not considered standard of care (See Section 4.3)
- Review eligibility criteria
- Review medical chart for past medical/surgical history
- Record medications and prior treatment regimen
- Record response to prior treatment regimen Document histopathology from:
  - Original diagnosis ○ Tumor biopsy in the relapsed setting
- Documentation of known measurable disease parameters by the following procedures:
  - CT of neck, chest, abdomen, and pelvis (PET/CT preferred but PET is optional)
  - Skin exam if known skin involvement ○ Other imaging techniques documenting disease site other than neck, chest, abdomen, and pelvis, if applicable
- Obtain a 12-lead electrocardiogram (ECG) and calculate the QTc interval.
- Perform a comprehensive physical examination
- Assess and record ECOG Performance Status
- Local laboratory: Collect blood for hematology (CBC with differential count), chemistry (Na, K, Cl, HCO3, BUN, creatinine, glucose, calcium, magnesium, lactate dehydrogenase, serum β-human chorionic gonadotropin [β-hCG] pregnancy test for women who are not postmenopausal or surgically sterile [within 7 days prior to cycle 1, dose 1 and again within 24 hours prior to first dose of the study drugs), liver function tests (total protein, albumin, AST, ALT, total bilirubin, direct bilirubin, and alkaline phosphatase).
- Calculate creatinine clearance using the glomerular filtration rate (GFR) according to the Cockroft and Gault Equation, only if screening serum creatinine is > 1.5 mg/dL.

4.3 INFORMED CONSENT

Study personnel must obtain documented consent from each potential patient prior to entering in a clinical study. Consent must be documented on the IRB approved consent form by obtaining

the dated signature both of the patient and of the investigator conducting the consent discussion. If the patient is unable sign the consent form, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., study staff personnel).

If the patient is legally incompetent (i.e., a minor or mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. An impartial witness will also sign such consent.

The information from the consent form should be translated and communicated to the subject in language understandable to the subject. Consent forms will be available in English and Spanish. When the study participant is non-English and non-Spanish speaking, the consent form must be read accurately in its entirety by a qualified professional translator. The translator will provide a written statement indicating that the consent form has been accurately translated from the accompanying English version, and that the study participant consents to participation.
The professional translator will sign the consent form as an impartial witness.

A copy of the signed and dated consent form should be given to the patient before participation in the study.

Patients may undergo study screening tests prior to giving written informed consent provided that these tests are considered part of standard care.

The initial informed consent form and any subsequent revised written informed consent form, and written information will receive the IRB approval. The patient or his/her legally acceptable representative will be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be documented.

4.3.1 CONSENT AND USE OF TISSUE SPECIMENS FOR RESEARCH

Patients who choose to participate in the optional biopsies will undergo a tissue biopsy pretreatment and a second biopsy between Day 8 and 21 of cycle 1. The investigator or designee is responsible for explaining and verifying the subject's consent before obtaining any biopsy. It will be explained to the patient that allowing the lymph node sample is encouraged, but optional, and participation in the associated clinical study is not dependent upon giving this sample.

4.4 REGISTRATION PROCESS

To register a patient, the following documents should be completed by a member of the research staff and delivered to the study coordinator:

- Eligibility Screening Worksheet
- Copy of required laboratory and imaging tests
- Signed patient consent forms
- HIPAA authorization form

The Study Coordinator will verify eligibility. To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Confirm registration with the principal investigator

5. TREATMENT PLAN

5.1 AGENT ADMINISTRATION

5.1.1 Regimen Description

Patients will be treated with TGR-1202 and carfilzomib administered as follows: TGR-1202 from Days 1-2[1]; and carfilzomib administered intravenously on Days 1, 8, 15 of a 28-day cycle (Table

REGIMEN DESCRIPTION					
Agent	**Premedications Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Carfilzomib	IV hydration, dexamethasone	20-56** mg/m^2	IV over 30 minutes	Days 1, 8, 15	28 days
TGR-1202		600-800 mg	Oral	Once daily on days 1-	
				21	
** Doses as appropriate for assigned dose level with the following exception: on cycle 1 day 1 of all assigned dose level carfilzomib is dosed at 20 mg/m^2. Premedication for carfilzomib includes hydration with 250-500 ml of normal saline, and dexamethasone 4mg to prevent infusion reaction.					

[1]).

Table 1: **Regimen Description**

5.1.2 Dose Escalation Scheme

In phase I, cohorts of 3 patients will be administered oral TGR-1202 and carfilzomib starting at 36 mg/m^2 for carfilzomib (note that the dose for c1d1 is 20 mg/m2). Oral TGR-1202 will be given at the fixed dose of 800 mg daily. Carfilzomib dose of 56 mg/m^2 (note that the dose for c1d1 is 20 mg/m2) representing the highest dose cohort. The dose levels to be considered are outlined in the escalation schema in Table 2. The rules for dose escalation or de-escalation are outline in Table 3.

Once the maximally tolerated dose (MTD) is reached the Phase Ib part of the protocol will be initiated in patients with R/R PTCL or C-MYC positive DLBCL (Figure 2).

Table 2: **Dose Escalation Scheme for the Combination of TGR-1202 and Carfilzomib**

Dose Escalation Schedule		
Dose Level	**Dose**	
	Carfilzomib (mg/m2) Given on days 1,8,15 of each 28-day cycle[(b)]	TGR-1202 (mg) Given once daily on days 1-21 of each 28-day cycle
Level -1[(a)]	20*/20	600
Level 1	20*/36	800
Level 2	20*/56	800
(a) In level -1, carfilzomib will be given at 20 mg/m2 on days 1, 8, 15 and TGR1202 on days 1-21.		

(b) For cycle 1 day 1 of each cohort, carfilzomib will be given at 20 mg/m2. If the treatment is tolerated, the drug will be given at the assigned dose level for all other treatment days involving carfilzomib.

Table 3. Dose Escalation & De-Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 additional patients experience DLT, proceed to the next dose level. • If 1 or more of this group experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose (MAD), and the dose level below is the MTD.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered).
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.1.3 REQUIRED BLOOD PARAMETERS AND OTHER INVESTIGATIONS PRIOR TO EACH TREATMENT

BEFORE THE START OF EACH TREATMENT, PATIENTS SHOULD BE REASSESSED AND THE FOLLOWING CRITERIA MUST BE FULFILLED:

- ANC > 1000/dL.
- Platelet count ≥ 50, 000/dL.
- Serum creatinine concentration ≤ 2.0 × ULN or ≤ baseline, or creatinine clearance >50 ml/min.
- AST (SGOT) and ALT (SGPT) ≤2.0 × ULN or ≤3.0 × ULN in presence of demonstrable liver metastases.
- Bilirubin concentration ≤2.0 × ULN.
- Recovery of any drug-related non-hematological toxicity to Grade 1 or less, unless otherwise indicated.

5.1.4 Guidelines for Study Drug Administration

- Oral TGR-1202 will be taken between the hours of 8 and 10 am daily (patient will be required to maintain a drug log recording side effects and time of dosage) on Days 1-21.

- Carfilzomib will be administered over 30 minutes through a peripheral or central venous catheter on Days 1, 8, 15 of a 28-day cycle. It will be administered within 6 hours of the oral dose. Premedication for carfilzomib includes hydration with 250-500 ml of normal saline, and dexamethasone 4mg to prevent infusion reaction.
- Administration of the study drugs will be allowed within 96 hours of the scheduled dates.
- Missed doses will not be made up.

5.1.5 Maximum Tolerated Dose

The dose-escalation rules and determination of the maximum tolerated dose (MTD) are outlined in Tables 2 and 3. Patients will be enrolled to receive oral TGR-1202 and carfilzomib in sequentially escalating doses until a maximum tolerated dose of the combination has been defined. The maximum tolerated dose of oral TGR-1202 and carfilzomib will be defined as the dose level immediately below the dose level at which greater than or equal to 2 patients out of 6 patients in a cohort experience a dose-limiting toxicity (DLT). Non-hematologic dose-limiting toxicity will be defined as any Grade 3, 4 or 5 non-hematologic toxicity, as explained further below:

- Grade 3 diarrhea that in the opinion of the Investigator occurs in the setting of inadequate compliance with supportive care measures specified in Section 5.1.7 and lasts for less than 48 hours.
- Grade 3 dehydration that in the opinion of the investigator, occurs in the setting of inadequate compliance with supportive care measures specified in Section 5.1.7 and lasts for less than 48 hours.
- Grade 3 acidosis or alkalosis that responds to medical intervention by returning to ≤ Grade 2 within 48 hours.
- Isolated (i.e. no other abnormalities) Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 4 days in duration.
- Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia that responds to medical intervention.
- Grade 3 Constipation
- Grade 3 Fatigue

5.1.6 Dose Limiting Toxicity

A dose limiting toxicity (DLT) is defined as any toxicity that occurs within cycle 1 and is considered at least “possibly related to study drug administration.” DLT is also defined as any toxicity possibly related to drug, occurring up to 4 days after completion of cycle 1 that results in a delay of initiating cycle 2. For patients who discontinue study drug administration after Cycle 1, DLT will be defined as any toxicity that occurs within 14 days of the last dose of drug on study, in cycle 1 that is considered at least possibly related to study drug.

DLTs include:

a. *Non-hematologic toxicity: All non-hematologic AEs of Grade 3 or greater with the exception of:*
    i. *Grade 3 nausea, vomiting controlled by supportive therapy*
    ii. *Any grade of alopecia.*
b. *Hematologic toxicity:*
    i. Grade 4 neutropenia lasting more than 4 days. ii. Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding or any requirement for platelets transfusion. iii. Grade 3 or greater febrile neutropenia (temperature ≥ 38.5ºC). iv. Grade 4 anemia unexplained by underlying disease.

5.2 DURATION OF TREATMENT

Patients will be treated until one of the following events:

- Disease progression
- Unacceptable adverse event(s), DLTs
- Withdrawal of consent
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy.

5.3 SAMPLE SIZE

Phase I

An estimated 9 patients (up to a maximum of 12) with R/R HL and NHL will be accrued to the Phase I study with 2 cohorts (Table 2). A minimum of 3 patients will be treated at each dose cohort. If no DLT is reached in cohort 3, then a total of 6 patients will be treated at that dose level.

Phase Ib

The expansion phase will accrue a total of 15 patients with R/R PTCL or C-MYC positive DLBCL (defined by 30% positive staining on IHC).

5.4 SAFETY

Patients will be monitored carefully for the development of adverse events as well as clinical and/or radiographic evidence of disease response. Adverse events will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

5.5 EFFICACY OUTCOME

Overall response rates will be evaluated using clinical parameters, CT scan (PET/CT scan is optional) and bone marrow biopsy, as outlined by the 2007 International Harmonization Project criteria and its update in 2014[1, 51].

5.6 PHARMACOKINETIC ANALYSES

On day 1 of cycle 1, blood samples will be obtained from patient's at fixed time intervals before and after administration of carfilzomib to determine the plasma level of both carfilzomib and TGR-1202. This will be compared to the known pharmacokinetic data for the individual agents in order to identify any possible effect of the combination. The proposed time points are shown in Figure 3.

SCHEMA

Figure 1. Drug Administration Schema

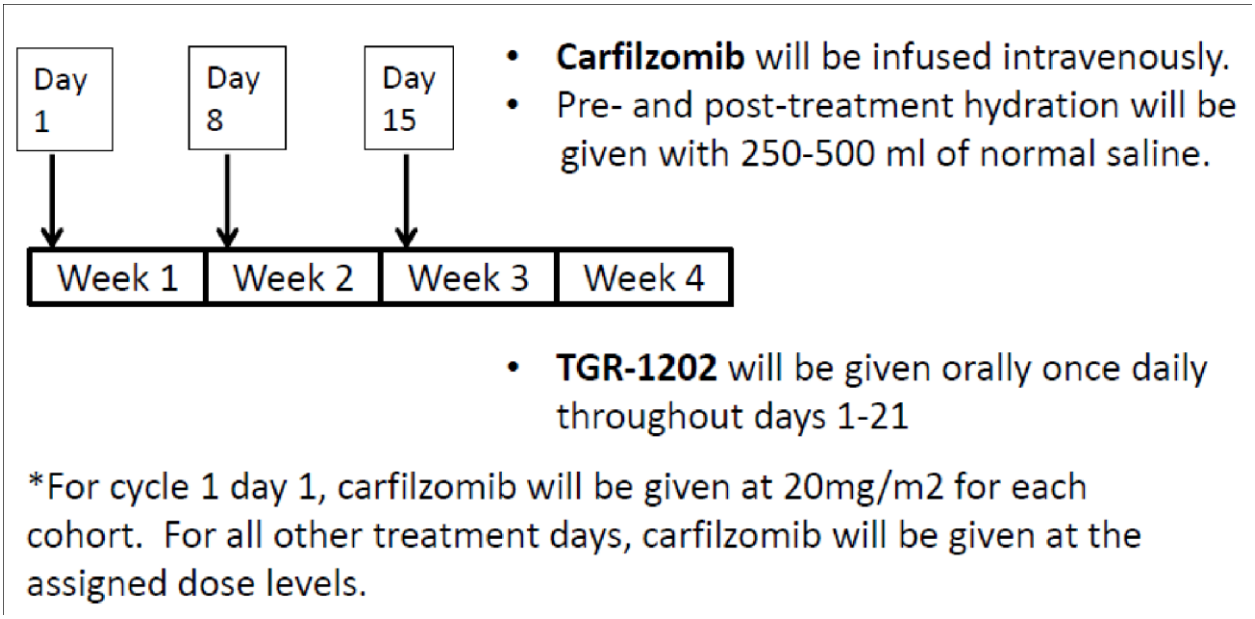


Figure 2: Study Plan Flow Chart Schema: Phase I

Screening

History, Physical, Performance Status,
Laboratory data, Biopsies, and CT scan (PET optional)

↓

CYCLE 1

Intervention

Oral TGR-1202 will be given PO once daily on Days 1-21 and carfilzomib given intravenously once a week for 3 consecutive weeks, on days 1, 8, 15 on the 28-day cycle.

Evaluations

Safety evaluations on Days 1, 8 , 15
Laboratory Evaluations Days 1,8,15
Follow -up Tissue Biopsy or Fine Needle Aspiration on Day 8 to 21 (optional)

↓

Future Cycles

Intervention

Oral TGR-1202 will be given PO once daily on Days 1-21 and carfilzomib given intravenously once a week for 3 con secutive weeks, on days 1, 8, 15 on the 28-day cycle.

Tests

Safety evaluations on Day 1
Laboratory Evaluations Days 1, 8, 15
CT scans at the end of Cycle 2 and 6. Then CT q3-6 months, until disease progression or initiation of new therapy at the discretio n of the Investigator. (PET is optional).

↓

Discontinuation

- Disease progression
- Unacceptable adverse event(s), DLTs
- Withdrawal of consent
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy.

Figure 3: Study Plan Flow Chart Schema: Phase II

Screening

History, Physical, Performance Status,
Laboratory data, Biopsies, and CT scan (PET optional)

↓

CYCLE 1

Intervention

Oral TGR-1202 will be given PO once daily on Days 1-21 and carfilzomib given intravenously once a week for 3 consecutive weeks, on days 1, 8, 15 on the 28-day cycle.

Evaluations

Safety evaluations on Days 1, 8, 15
Laboratory Evaluations Days 1,8,15
Follow-up Tissue Biopsy or Fine Needle Aspiration on Day 8 to 21 (optional)

↓

Future Cycles

Intervention

Oral TGR-1202 will be given PO once daily on Days 1-21 and carfilzomib given intravenously once a week for 3 consecutive weeks, on days 1, 8, 15 on the 28-day cycle.

Tests

Safety evaluations on Day 1

Laboratory Evaluations Days 1, 8, 15

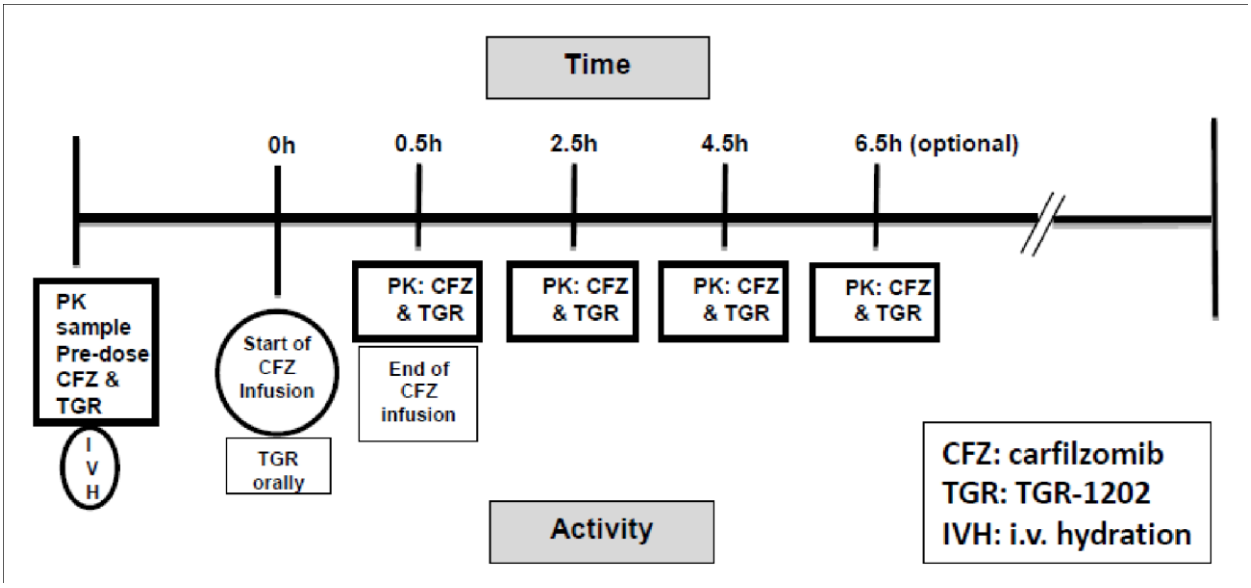
CT scans at the end of Cycle 2 and 6. Then CT q3-6 months, until disease progression or initiation of new therapy at the discretion of the Investigator. (PET is optional).

↓

Discontinuation

- Disease progression
- Unacceptable adverse event(s), DLTs
- Withdrawal of consent
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy.

Figure 4. PK Studies on Cycle 1 Day 1



5.7 PROPHYLACTIC MEDICINES AND SUPPORTIVE CARE

Standard institutional guidelines for anti-emetics will be used. Supportive treatment may include additional anti-emetics, anti-diarrheal, anti-pyretics, anti-histamines, analgesics, antibiotics, and blood products.

For cycle 1 of the phase 1, prophylactic G-CSF will not be administered with the following exception: if neutropenia is identified as a DLT at dose level 1 in cycle 1 of phase 1, then all subsequent patients will receive G-CSF prophylactically daily for up to 3 days in weeks 1, 2, and 3, and up to 7 days in week 4 of the 28-day cycle. When needed, G-CSF should be given 24 hours after the administration of carfilzomib. For patients in the phase 2, prophylactic G-CSF can be given at the physician's discretion. Neulasta should only be given if there is a 14 day interval to the next dose.

Post cycle 1, anemia may be managed with growth factors according to the ASCO guidelines: 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline http://www.jco.org/cgi/content/full/24/19/3187.

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- Diarrhea: Diarrhea should be treated promptly with appropriate supportive care, including loperamide. Loperamide should not be taken prophylactically. Patients should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool.
- Nausea/vomiting: Carfilzomib and TGR-1202 are minimally emetigenic.
- Nausea and vomiting should be treated per standard practice guidelines, with agents such as prochlorperazine, metoclopramide, 5-HT-3 inhibitors, or benzodiazepines. Patients should be strongly encouraged to maintain liberal oral fluid intake during

therapy. Fatigue: May be cumulative with increasing cycles of therapy. Can be treated as indicated by the treating physician.

- Anemia: TGR-1202 and carfilzomib have been associated with dose-related anemia. Transfusions or erythropoetin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.
- Thrombocytopenia: Treatment with TGR-1202 and carfilzomib can cause dose-related thrombocytopenia. Transfusion of platelets may be used if clinically indicated. Dose modification for thrombocytopenia is allowed in a manner consistent with the guidelines for dose modification (Section [6.3]).
- Neutropenia: Prophylactic use of colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF should not be utilized during the first cycle of therapy. These factors may be utilized if clinically indicated in subsequent cycles.

5.8 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

There is no evidence of interaction TGR-1202 or carfilzomib with other concomitantly administered drugs through the cytochrome P450 system.

Prohibited concurrent therapy

 Concomitant use of other anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving protocol therapy during the treatment phase of the study.

PROPHYLACTIC MEASURES

Subjects should receive allopurinol and other treatment considered appropriate for tumor lysis prophylaxis in cycle 1 as deemed necessary by the treating physician.

For cycle 1 of the phase 1, prophylactic G-CSF will not be administered with the following exception: if neutropenia is identified as a DLT at dose level 1 in cycle 1 of phase 1, then all subsequent patients will receive G-CSF prophylactically daily for up to 3 days in weeks 1, 2, and 3, and up to 7 days in week 4 of the 28-day cycle. When needed, G-CSF should be given 24 hours after the administration of carfilzomib. For patients in the phase 2, prophylactic G-CSF can

be given at the physician's discretion. Neulasta should only be given if there is a 14 day interval to the next dose.

5.9 DURATION OF THERAPY

Treatment may continue until one of the following criteria applies:

- Disease progression
- Unacceptable adverse event(s), DLTs
- Withdrawal of consent
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy

5.10 DURATION OF FOLLOW UP

Patients will have an end of study visit 4 weeks (+/- 2 weeks) after their last dose of drug to evaluate safety. Patients will be followed every 3 to 4 months after the 4-week safety evaluation for one year, or until they begin a new treatment for their disease, for evaluation of delayed toxicity. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow up visits will include toxicity assessments, review of concomitant medications, physical examinations, and blood work (including a CBC with differential and chemistries).

CT scans (PET/CT optional) will not be routinely used to monitoring complete responses after 6 months, but rather, will be used when indicated, due to concern for disease progression.

5.11 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from treatment when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator will notify the appropriate parties within 2 business days when a subject has been discontinued/ withdrawn due to an adverse event. When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse events present at the time of discontinuation/withdrawal will be followed until resolution.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 DOSE DELAYS

- Study drugs can be administered within 96 hours of their scheduled time.
- Study drugs will be held for DLTs until adverse event returns to ≤ Grade 2.
- If interruption lasts for more than 14 days, study treatment will be discontinued.

6.2 RESUMING ADMINISTRATION OF STUDY DRUGS

For toxicities that can be treated or prevented, such as nausea, vomiting, diarrhea and neutropenia, treatment may be resumed at the previous dose once supportive measures have been instituted and toxicity recovers to Grade 2 or less.

6.3 DOSE MODIFICATIONS

If TGR-1202 and carfilzomib administration leads to a DLT beyond cycle 1 at a given dose level, dose modifications will be managed by dropping one dose level in the dose escalation scheme. These post Cycle 1 DLTs will not count towards the overall determination of MTD for this study.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 SAFETY EVALUATION PROCEDURES

Adverse Event Reporting

An adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drugs, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drugs product, is also an adverse event.

Adverse events may occur in the course of receiving study drugs or within the follow-up period specified by the protocol, as well as from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.0. Toxicities will be characterized in terms including duration, intensity, and time to onset. Safety endpoints will include all types of adverse events, in addition to laboratory safety assessments, ECOG performance scale status, ECGs, and vital signs.

The investigator must assess all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

The following safety evaluations will be performed during patient screening and at defined points during the course of the study:

- Vital signs
- Laboratory studies complete blood count (CBC), serum chemistry, urinalysis, coagulation studies (PT/PTT), pregnancy test, LDH
- Electrocardiograms (ECG)
- Physical examinations
- Performance Status Evaluation using the ECOG scale
- Adverse event monitoring using the NCI CTCAE v4.0

Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening1
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity2
- Is a congenital anomaly or birth defect
- Is an important medical event3
- Pregnancy

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

2“Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.

3Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Hospitalizations that do not meet these criteria are:

- reasons described in the protocol, e.g., drug administration, protocol-required testing
- social reason in the absence of an AE
- surgery or procedure planned prior to entry into the trial

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.2) and the characteristics of an observed AE (Section 7.3) will determine whether the event requires expedited (via AdEERS) in addition to routine reporting.

Ongoing monitoring of the clinical safety data in this trial will be performed consistent with procedures outlined in the DSMC charter. This review will pay particular attention to Grade 3 or 4 adverse events, serious adverse events (SAEs), adverse events that lead to discontinuation and adverse events that lead to dose reduction. Should the incidence of any particular adverse event, or combination of events, rise to a level of clinical concern the DSMC will be notified for possible review of the emergent adverse events.

7.2 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS) OF TGR-1202

The following adverse events were observed in patients treated with single agent TGR-1202 and were considered at least possibly related to study medication. See the TGR-1202 investigator brochure for a complete list of all adverse events reported regardless of causality.

[redacted]

- Blood and lymphatic system disorders: Neutropenia,

- Gastrointestinal disorders: Nausea, Diarrhea, Vomiting, Abdominal pain, Constipation
- General disorders and administration site conditions: Fatigue
- Metabolism and nutrition disorders: Decreased appetite, Hypokalemia
- Nervous system disorders: Headache, Dizziness
- Respiratory, thoracic, and mediastinal disorders: Cough, Dyspnea Skin and subcutaneous tissue disorders: Rash

[redacted]

- Blood and lymphatic system disorders: Anemia, Leukocytosis, Thrombocytopenia
- Eye Disorders: Vision blurred
- Gastrointestinal disorders: Abdominal distension, Dry mouth, Dyspepsia, Eructation, Mouth ulceration
- General disorders and administration site conditions: Asthenia, Chills, Malaise, edema Peripheral, Pyrexia
- Hepatobiliary Disorders: Hyperbilirubinemia
- Infections and infestations: Candida infection, Lung infection, Oral candidiasis, Pneumonia, Urinary tract infection
- Investigations: Blood creatinine increased, Blood lactate dehydrogenase increased, Blood phosphorus increased, Blood sodium increased, Lymphocyte count increased, Platelet count decreased, Weight decreased
- Metabolism and nutrition disorders: Dehydration, Hyperglycemia, Hyperlipidemia, Hyponatremia, Hypophosphatemia
- Musculoskeletal and connective tissue disorders: Arthralgia, Muscle spasms, Muscular weakness, Myalgia, Pain in extremity
- Nervous system disorders: Dysgeusia, Somnolence, Tremor
- Psychiatric Disorders: Libido decreased
- Respiratory, thoracic, and mediastinal disorders: Epistaxis, Hypoxia, Respiratory failure
- Skin and Subcutaneous Tissue Disorders: Alopecia, Dermatitis acneiform, Night sweats, Pruritus, Rash Maculo-Papular, Rash pruritic

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:

- Liver Disorders: Elevated levels of certain liver enzymes
- Brain and nerve related disorders: Paresthesia
- Kidney disorders: Elevated blood urea nitrogen levels, Elevated phosphorus, Hyperuricemia
- Breathing and chest related disorders: Nasal congestion, Upper respiratory tract infection
- General disorders: Arthralgia, Myalgia
- Infections and Infestations: Infection

7.3 CAEPRS OF CARFILZOMIB

Table 4 lists adverse drug reactions reported in subjects receiving carfilzomib for which there is a reasonable possibility of a causal relationship to carfilzomib. In addition, special warnings and precautions are required for the conditions described in Section 7.3.1-7.3.9.

Table 4. Adverse Drug Reactions of Carfilzomib

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade 3 and Above Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Blood and lymphatic system disorders			
Anemia	725 (45.9%)	356 (22.5%)	30 (1.9%)
Thrombocytopenia	552 (34.9%)	367 (23.2%)	25 (1.6%)
Neutropenia	376 (23.8%)	249 (15.7%)	10 (0.6%)
Lymphopenia	198 (12.5%)	156 (9.9%)	-
Leukopenia	162 (10.2%)	68 (4.3%)	2 (0.1%)
Febrile neutropenia	35 (2.2%)	29 (1.8%)	26 (1.6%)
TTP/HUS[a,b]	-	-	-
Cardiac disorders			
Cardiac failure[c]	69 (4.4%)	46 (2.9%)	44 (2.8%)
Myocardial infarction	12 (0.8%)	10 (0.6%)	9 (0.6%)
Cardiac arrest	9 (0.6%)	9 (0.6%)	9 (0.6%)
Myocardial ischemia	6 (0.4%)	4 (0.3%)	4 (0.3%)
Eye disorders			
Vision blurred	81 (5.1%)	1 (< 0.1%)	-
Cataract	41 (2.6%)	16 (1.0%)	2 (0.1%)
Gastrointestinal disorders			
Diarrhea	533 (33.7%)	37 (2.3%)	13 (0.8%)
Nausea	505 (31.9%)	14 (0.9%)	2 (0.1%)
Constipation	292 (18.5%)	3 (0.2%)	-
Vomiting	270 (17.1%)	9 (0.6%)	3 (0.2%)
Abdominal pain[c]	168 (10.6%)	19 (1.2%)	10 (0.6%)
Dyspepsia	92 (5.8%)	2 (0.1%)	-
Toothache	39 (2.5%)	2 (0.1%)	-
General disorders and administration site conditions			
Fatigue	689 (43.6%)	94 (5.9%)	1 (< 0.1%)
Pyrexia	446 (28.2%)	25 (1.6%)	46 (2.9%)
Edema peripheral	344 (21.8%)	10 (0.6%)	1 (< 0.1%)
Asthenia	189 (12.0%)	26 (1.6%)	4 (0.3%)
Chills	167 (10.6%)	2 (0.1%)	2 (0.1%)
Pain	110 (7.0%)	21 (1.3%)	9 (0.6%)

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade 3 and Above Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
General disorders and administration site conditions (continued)			
Multi-organ failure	8 (0.5%)	8 (0.5%)	7 (0.4%)
Infusion site reaction	3 (0.2%)	-	-
Infusion reactions[d]	-	-	-
Hepatobiliary disorders			
Hepatic failure	2 (0.1%)	1 (< 0.1%)	1 (< 0.1%)
Infections and infestations			
Respiratory tract infection[c]	414 (26.2%)	49 (3.1%)	31 (2.0%)
Pneumonia	197 (12.5%)	147 (9.3%)	153 (9.7%)
Nasopharyngitis	157 (9.9%)	1 (< 0.1%)	1 (< 0.1%)
Bronchitis	115 (7.3%)	16 (1.0%)	18 (1.1%)
Urinary tract infection	111 (7.0%)	21 (1.3%)	14 (0.9%)
Influenza	58 (3.7%)	5 (0.3%)	7 (0.4%)
Sepsis	29 (1.8%)	27 (1.7%)	23 (1.5%)
Viral infection	27 (1.7%)	-	1 (< 0.1%)
Investigations			
Blood creatinine increased	246 (15.6%)	37 (2.3%)	8 (0.5%)
Aspartate aminotransferase increased	107 (6.8%)	31 (2.0%)	2 (0.1%)
Alanine aminotransferase increased	95 (6.0%)	38 (2.4%)	2 (0.1%)
Blood uric acid increased	54 (3.4%)	17 (1.1%)	-
Creatinine renal clearance decreased	28 (1.8%)	3 (0.2%)	-
C-reactive protein increased	20 (1.3%)	4 (0.3%)	-
Metabolism and nutrition disorders			
Hypokalemia	250 (15.8%)	75 (4.7%)	4 (0.3%)
Decreased appetite	239 (15.1%)	4 (0.3%)	-
Hyperglycemia	211 (13.3%)	68 (4.3%)	5 (0.3%)
Hypomagnesemia	162 (10.2%)	9 (0.6%)	-
Hypocalcemia	153 (9.7%)	38 (2.4%)	3 (0.2%)

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade 3 and Above Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Metabolism and nutrition disorders (continued)			
Hypophosphatemia	148 (9.4%)	88 (5.6%)	1 (< 0.1%)
Hyponatremia	122 (7.7%)	68 (4.3%)	5 (0.3%)
Hypercalcemia	116 (7.3%)	43 (2.7%)	30 (1.9%)
Hyperuricemia	93 (5.9%)	24 (1.5%)	-
Hyperkalemia	80 (5.1%)	22 (1.4%)	3 (0.2%)
Hypoalbuminemia	80 (5.1%)	31 (2.0%)	1 (< 0.1%)
Dehydration[a]	64 (4.0%)	16 (1.0%)	11 (0.7%)
Tumor lysis syndrome[a]	11 (0.7%)	10 (0.6%)	10 (0.6%)
Musculoskeletal and connective tissue disorders			
Back pain	300 (19.0%)	44 (2.8%)	13 (0.8%)
Muscle spasms	252 (15.9%)	8 (0.5%)	-
Arthralgia	229 (14.5%)	16 (1.0%)	2 (0.1%)
Pain in extremity	202 (12.8%)	16 (1.0%)	3 (0.2%)
Musculoskeletal pain	155 (9.8%)	23 (1.5%)	2 (0.1%)
Musculoskeletal chest pain	139 (8.8%)	6 (0.4%)	2 (0.1%)
Muscular weakness	98 (6.2%)	18 (1.1%)	4 (0.3%)
Myalgia	90 (5.7%)	5 (0.3%)	-
Nervous system disorders			
Headache	323 (20.4%)	17 (1.1%)	4 (0.3%)
Dizziness	184 (11.6%)	9 (0.6%)	1 (< 0.1%)
Neuropathy peripheral[a]	137 (8.7%)	16 (1.0%)	1 (< 0.1%)
Paresthesia	131 (8.3%)	3 (0.2%)	1 (< 0.1%)
Hypoesthesia	109 (6.9%)	2 (0.1%)	-
PRES[a,b]	-	-	-
Psychiatric disorders			
Insomnia	255 (16.1%)	11 (0.7%)	-
Anxiety	105 (6.6%)	4 (0.3%)	-

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade 3 and Above Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Renal and urinary disorders			
Renal failure acute	94 (5.9%)	71 (4.5%)	70 (4.4%)
Renal failure	53 (3.4%)	25 (1.6%)	15 (0.9%)
Renal impairment	25 (1.6%)	9 (0.6%)	4 (0.3%)
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	436 (27.6%)	63 (4.0%)	33 (2.1%)
Cough	383 (24.2%)	4 (0.3%)	2 (0.1%)
Epistaxis	125 (7.9%)	7 (0.4%)	3 (0.2%)
Oropharyngeal pain	123 (7.8%)	-	-
Dysphonia	41 (2.6%)	-	-
Pulmonary edema	26 (1.6%)	16 (1.0%)	15 (0.9%)
Pulmonary embolism	24 (1.5%)	20 (1.3%)	21 (1.3%)
Skin and subcutaneous tissue disorders			
Rash[a]	127 (8.0%)	8 (0.5%)	5 (0.3%)
Pruritus	93 (5.9%)	1 (< 0.1%)	-
Erythema	71 (4.5%)	-	-
Hyperhidrosis	62 (3.9%)	-	-
Vascular disorders			
Hypertension	236 (14.9%)	69 (4.4%)	10 (0.6%)
Hypotension	89 (5.6%)	23 (1.5%)	15 (0.9%)
Deep vein thrombosis	49 (3.1%)	19 (1.2%)	17 (1.1%)

ADR = adverse drug reaction; PRES = posterior reversible encephalopathy syndrome; PT = preferred term; TLS = tumor lysis syndrome; TTP/HUS = thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

[a] The following ADRs were reported in the postmarketing experience: dehydration, peripheral neuropathy, rash, TTP/HUS, TLS including fatal outcomes, and PRES.

[b] Not reported in the pooled clinical studies dataset. The maximum frequency for this ADR can be estimated per standard practice from the upper limit of 95% confidence interval for the point estimate, i.e., 3/1581 (or 0.19%) as zero subjects reported these events in the pooled clinical studies dataset.

[c] The following clinically related terms have been grouped together and the total subject incidence of the grouped terms is reported: abdominal pain includes PTs of abdominal pain and

upper abdominal pain, cardiac failure includes PTs of cardiac failure and congestive cardiac failure, and respiratory tract infection includes PTs of respiratory tract infection and upper respiratory tract infection.

[d] Not a specific PT. This was analyzed by grouping together systemic symptoms such as pyrexia, chills, and dyspnea. Adverse events of asthenia, arthralgia, chills, dyspnea, myalgia, pyrexia, and vomiting that were analyzed as part of this grouping are also separately called out as ADRs.

7.3.1 CARDIOPULMONARY DISORDERS

New or worsening cardiac failure (e.g., congestive cardiac heart failure, pulmonary edema, and decreased ejection fraction), myocardial ischemia, and myocardial infarction have occurred following administration of carfilzomib. Death due to cardiac arrest has occurred within a day of carfilzomib administration, and fatal outcomes have been reported with cardiac failure and myocardial infarction.

While adequate hydration is required prior to dosing in Cycle 1, all subjects should be monitored for evidence of volume overload, especially subjects at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in subjects with baseline cardiac failure or who are at high risk for cardiac failure.

Withhold carfilzomib for Grade 3 or 4 cardiac events until recovery and consider whether to restart carfilzomib at 1 dose level reduction based on a benefit/risk assessment.

Refer to the study protocol for further instructions regarding dose modifications.

The risk of cardiac failure is increased in elderly subjects (≥ 75 years).

Subjects with New York Heart Association Class II-IV heart failure, recent myocardial infarction (within 6 months), and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These subjects may be at greater risk for cardiac complications.

Dyspnea, predominantly Grade 1 and 2, has been reported in subjects enrolled in clinical trials. Evaluate subjects with dyspnea based on the clinical presentation and manage accordingly. Reduce or withhold dose as appropriate. Refer to the study protocol for further instructions regarding dose modifications.

7.3.2 ACUTE RENAL FAILURE

Cases of acute renal failure have been reported in subjects who received carfilzomib. Acute renal failure was reported more frequently in subjects with advanced relapsed and refractory multiple myeloma who received carfilzomib monotherapy. This risk was increased in subjects with a decrease in estimated creatinine clearance, calculated using Cockcroft and Gault equation, prior to receiving carfilzomib. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance.

Reduce or withhold dose as appropriate. Refer to the study protocol for further instructions regarding dose modifications.

7.3.3 TUMOR LYSIS SYNDROME

Cases of TLS, including fatal outcome, have been reported in subjects who received carfilzomib. Subjects with a high tumor burden should be considered to be at greater risk for TLS. Ensure that subjects are well hydrated before administration of carfilzomib in Cycle 1 and in subsequent cycles as needed. Uric acid-lowering drugs should be considered in subjects at high risk for TLS. Monitor for evidence of TLS during treatment, including regular measurement of serum electrolytes, and manage promptly. Interrupt carfilzomib until TLS is resolved. Refer to the study protocol for further instructions regarding dose modifications.

7.3.4 INFUSION REACTIONS

Infusion reactions, including life-threatening reactions, have been reported in subjects who received carfilzomib. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Administer dexamethasone prior to carfilzomib either as premedication or as part of combination therapy to reduce the incidence and severity of reactions. Refer to the study protocol for further instructions regarding dose modifications.

7.3.5 THROMBOCYTOPENIA

Carfilzomib causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle with recovery to baseline platelet count by the start of the next cycle. Monitor platelet counts frequently during treatment with carfilzomib. Reduce or withhold dose as appropriate. Refer to the study protocol for further instructions regarding dose modifications.

7.3.6 HEPATIC TOXICITY

Cases of hepatic failure, including fatal cases, have been reported. Carfilzomib can cause elevations of serum transaminases. Monitor liver enzymes regularly. Reduce or withhold dose as appropriate. Refer to the study protocol for further instructions regarding dose modifications.

7.3.7 THROMBOCYTOPENIC THROMBOTIC PURPURA/HEMOLYTIC UREMIC SYNDROME

Cases of thrombocytopenic thrombotic purpura/hemolytic uremic syndrome (TTP/HUS) including those with fatal outcome have been reported in subjects who received carfilzomib. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop carfilzomib and manage per

standard of care including plasma exchange as clinically appropriate. If the diagnosis of TTP/HUS is excluded, carfilzomib can be restarted. Refer to the study protocol for further instructions regarding dose modifications. The safety of reinitiating carfilzomib therapy in subjects previously experiencing TTP/HUS is not known.

7.3.8 POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension.

The diagnosis is confirmed by neuro-radiological imaging. If diagnosed early and treated, the symptoms of PRES may be reversed. Cases of PRES have been reported in subjects receiving carfilzomib. Discontinue carfilzomib if PRES is suspected. Refer to the study protocol for further instructions regarding dose modifications. The safety of reinitiating carfilzomib therapy in subjects previously experiencing PRES is not known.

7.3.9 PULMONARY HYPERTENSION

In Phase 2 studies, pulmonary arterial hypertension was reported in 2% of subjects treated with carfilzomib and was Grade 3 or greater in less than 1% of subjects. In the pooled safety data from studies where carfilzomib was used in combination with lenalidomide-dexamethasone and in monotherapy studies (with or without dexamethasone) (N = 1581), events within the narrow pulmonary hypertension standardized Medical Dictionary for Regulatory Activities (MedDRA) query were reported in 1.1% of subjects. However, the incidence of pulmonary hypertension was similar across treatment groups in randomized, controlled studies where carfilzomib was used in combination with lenalidomide-dexamethasone and also in monotherapy studies (with or without dexamethasone). Therefore, a causal relationship with carfilzomib has not been demonstrated and pulmonary hypertension is considered an important potential risk. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months,

and conduction abnormalities uncontrolled by medications were excluded from clinical studies with carfilzomib, as they may be at greater risk of cardiopulmonary complications.

Monitor subjects for signs and symptoms of pulmonary hypertension. Evaluate with cardiac imaging and/or other tests as indicated. Withhold carfilzomib until resolved or returned to baseline and consider whether to restart carfilzomib based on a risk/benefit assessment.

7.4 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. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- 'Expectedness': AEs can be 'Unexpected' or 'Expected' (see Section 7.2 above) for expedited reporting purposes only.
- 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.

7.5 EXPEDITED ADVERSE EVENT REPORTING

The Principal Investigator agrees to provide appropriate parties with copies of all serious adverse experiences*, within two working days. Additionally, the Principal Investigator agrees to report any pregnancy occurring in association with use of an oral TGR-1202 and carfilzomib to the appropriate parties.

Expedited reporting by investigator to TG Therapeutics:

Serious adverse events (SAE) are defined above. All SAEs will be reported within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to TGR-1202.

TG Therapeutics, Inc.
2 Gansevoort Street, 9th Floor
New York, NY 10014
Tel: 212-554-4484
Fax: 212-554-4531

Expedited reporting by investigator to Amgen:

Amgen Medical Information
800-77-AMGEN (800-772-6436)

The initial SAE report must be as complete as possible, including details of the current illness and (serious) AE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented on a follow-up form. All follow-up information must be reported in the same timelines as initial information.

At any time after completion of the AE reporting period (i.e., 30 days post-treatment), if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to one of the study drugs, the event must be reported to Infinity Drug Safety.

Report of Adverse Events to the Institutional Review Board

Reportable information should always be reported by the PI directly to the IRB within 5 working days from when the PI learns of the event or new information.

Investigator Reporting to the FDA

The investigator is responsible for reporting any SAEs to the FDA. Serious adverse events (SAEs) that are unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone (1-800-332-1088), fax (1-800-FDA-0178), or via MedWatch Online. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Adverse event updates/IND safety reports

Both sponsor shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Amgen, TG Therapeutics, and the IRB/EC, on file (see Section 12 for records retention information).

7.5.1 EXPEDITED REPORTING GUIDELINES

Note: All deaths on study require expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

Expedited AE reporting timelines defined:

- "1 business day; 5 calendar days" – The investigator must initially report the AE within 1 business day of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported if the event occurs following treatment.

7.5.2 PROTOCOL-SPECIFIC EXPEDITED ADVERSE EVENT REPORTING EXCLUSIONS

For this protocol, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting. The following AEs must be reported through the routine reporting mechanism (Section 7.7):

Table 5: CTCAE AE Reporting Exclusions

CTCAE Category	Adverse Event	Grade	Hospitalization / Prolongation of Hospitalization	Attribution
Blood/Bone Marrow	Neutropenia <7 days without fever	4	No	Yes
Blood/ Bone Marrow	Thrombocytopenia <7 days without bleeding	4	No	Yes

7.6 PREGNANCY ON STUDY

No studies of carfilzomib have been conducted in pregnant women. Carfilzomib should not be used during pregnancy.

Pregnant women and women planning to become pregnant may NOT participate in clinical trials with carfilzomib.

Females

Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. Given that carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, as a precaution, females with childbearing potential and/or male partners should use effective contraception methods or abstain from sexual activity while treated with carfilzomib during and for 30 days following treatment. Based on its mechanism of action and findings in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. If carfilzomib is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Carfilzomib administered to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats or up to 0.8 mg/kg/day in rabbits. Refer to the study protocol for specific information regarding length of time contraception should be used and acceptable contraceptive methods.

Males

The potential for carfilzomib to be transferred via semen and its effect on sperm are unknown. Refer to the study protocol for specific information regarding length of time contraception should be used and acceptable contraceptive methods for studies that require male contraception. Male subjects should be advised to inform the investigator or study staff immediately in the event that their female partner becomes pregnant during the study. Upon receipt of this information, the investigator should notify Amgen of the pregnancy and discuss follow-up regarding the pregnancy outcome with the subject.

7.7 ROUTINE ADVERSE EVENT REPORTING

All Adverse Events must be reported in routine study data submissions.

For 30 days subsequent to study completion or withdrawal, new onset adverse events will be captured. Follow up of these events will follow the same procedure as described above for AEs observed during the study period.

8. PHARMACEUTICAL INFORMATION

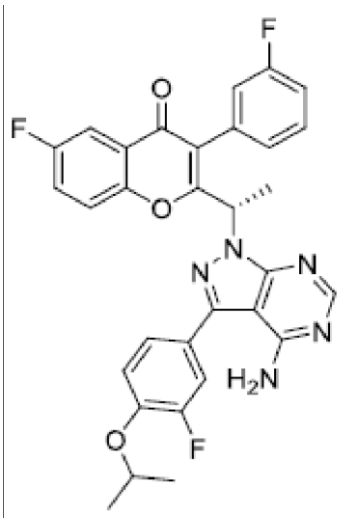
8.1 TGR-1202

Product description:

TGR-1202 is a highly specific and orally available PI3K delta inhibitor. TGR-1202 is manufactured by Alembic Pharmaceuticals and supplied by TG Therapeutics, Inc. TGR-1202 is supplied in 50, 100, and 200 mg tablets.

TGR-1202 is an isoflavone substituted pyrazolo pyrimidine. It is a p-Toluene sulphonic acid (p-TSA) salt of RP-5264 (base of TGR-1202).

- Description: Light brown to brown colored powder
- Solubility: Freely soluble in dimethyl sulfoxide and soluble in methanol

Chemical Structure: 

Stability: TGR-1202 is stored at temperatures not exceeding 25°C (excursions permitted to 15°C-25°C). Based on the results available on date a shelf life of 12 months is proposed for the drug product with revised primary packaging (inclusion of cotton). Further stability studies are ongoing and a retest period will be proposed for the drug product upon review of accumulated stability data.

Further stability testing is in progress at the below ICH conditions as per the established stability protocol and will be updated as available.

Administration:

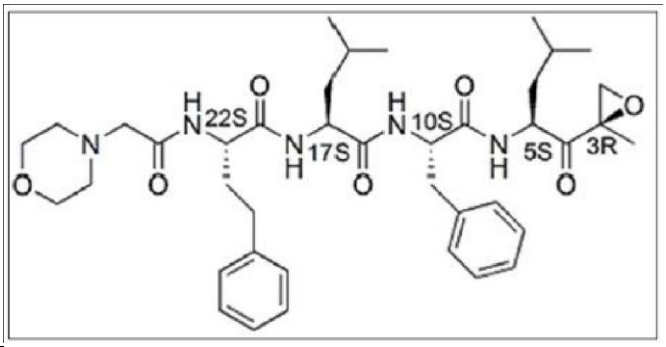
TGR-1202 will be administered daily for 21 days of every 28-day cycle. TGR-1202 is administered orally as a tablet formulation and will be supplied free of charge by TG Therapeutics. TGR-1202 will be administered as a fixed dose in 800 mg/day and should be administered using the minimal number of tablet necessary.

8.2 CARFILZOMIB

8.2.1 CARFILZOMIB PRODUCT DESCRIPTION

Generic Name: Carfilzomib is the generic name; formerly referred to as PR-171. Chemical Name: (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4methylpentanamide.

Molecular Formula: C40H57N5O7 Molecular Weight: 719.9

Chemical Structure: 

Pharmacologic Class: Antineoplastic agent

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that selectively and irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome, and displays little to no activity against other protease classes.

8.2.2 CARFILZOMIB DOSAGE FORM

Carfilzomib for Injection, 60 mg/vial, is supplied as a white to off white lyophilized cake or powder in a single-use vial. Prior to administration, the lyophilized product is aseptically reconstituted with 29 mL Sterile Water for Injection.

Reconstituted carfilzomib drug product consists of 2 mg/mL carfilzomib, 100 mg/mL sulfobutylether-beta-cyclodextrin, and 1.9 mg/mL citrate buffer (pH 3 to 4). Each mL of reconstituted drug product contains 0.3 mmol (7 mg) of sodium.

8.2.3 DRUG SUPPLY AND STORAGE

8.2.3.1 LYOPHILIZED DRUG PRODUCT

Lyophilized carfilzomib for Injection vials must be kept in the labeled drug cartons and stored at 2°C to 8°C (36°F to 46°F) in a refrigerator.

Vials must be kept in cartons in order to protect from light until ready for reconstitution.

- The refrigerator should be monitored daily (at a minimum) and temperature records retained for review.
- The refrigerator should also be on a backup generator whenever possible and also alarmed for temperature deviations.

Any temperature excursions during storage must be reported to Amgen for evaluation and disposition. Any product impacted by temperature excursions should be placed in quarantine pending completion of the Amgen evaluation and disposition. Any temperature excursion should be reported to Amgen using a temperature excursion form. The incident should be documented in the carfilzomib dispensation and accountability log. If the product must be destroyed, the vials should be destroyed per the site standard operating procedures. If drug destruction is unavailable at the site, the study monitor should be contacted for further instructions.

8.2.3.2 RECONSTITUTED DRUG PRODUCT

Once a drug vial is reconstituted and inspected for particulate matters, the clear and free of particles solution can be stored in a refrigerator (recommended) controlled from 2°C to 8°C (36°F to 46°F).

Reconstituted carfilzomib drug product must be used within 24 hours of reconstitution when kept at 2°C to 8°C (36°F to 46°F). If kept at room temperature after reconstitution, it must be used within 4 hours.

8.2.3.3 DO NOT FREEZE LYOPHILIZED OR RECONSTITUTED DRUG

If reconstituted carfilzomib drug product has been frozen, the material should be discarded and a new solution prepared. The damaged material should be documented on the Carfilzomib Investigational Product Accountability Log.

Amgen should be contacted by email for any questions regarding drug storage. The country, site number, protocol number, and detailed question(s) should be included in the correspondence.

8.2.3.4 METHOD OF ADMINISTRATION

Carfilzomib is administered intravenously (IV) as an infusion. Carfilzomib should not be administered as a bolus. Refer to the study protocol for specific information regarding length of time for infusion. The intravenous administration line should be flushed with normal saline or 5% dextrose injection immediately before and after carfilzomib administration. Do not mix carfilzomib with or administer as an infusion with other medicinal products.

Carfilzomib is administered once each week for 3 weeks (Days 1, 8, 15), followed by a 13-day rest period (Days 16 to 28), except when specified by the study protocol (Figure 1 and Table 1). Each 28-day period is considered 1 treatment cycle.

Refer to the study protocol for specific information on calculating the dose. It is recommended that the dose is calculated using the subject's baseline body surface area (BSA). Subjects with a BSA greater than 2.2 m2 should receive a dose based upon a BSA of 2.2 m2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.

Adequate hydration is required prior to dosing in Cycle 1, especially in subjects at high risk of tumor lysis syndrome (TLS) or renal toxicity. All subjects should be monitored for evidence of volume overload and fluid requirements should be tailored to individual subject needs. The total volume of fluids may be adjusted as clinically indicated in subjects with baseline cardiac failure or who are at high risk for cardiac failure (see Section 3.0, Special Warnings and Precautions for Use).

Consider antiviral prophylaxis in subjects being treated with carfilzomib to decrease the risk of herpes zoster reactivation.

8.3 AGENT ACCOUNTABILITY

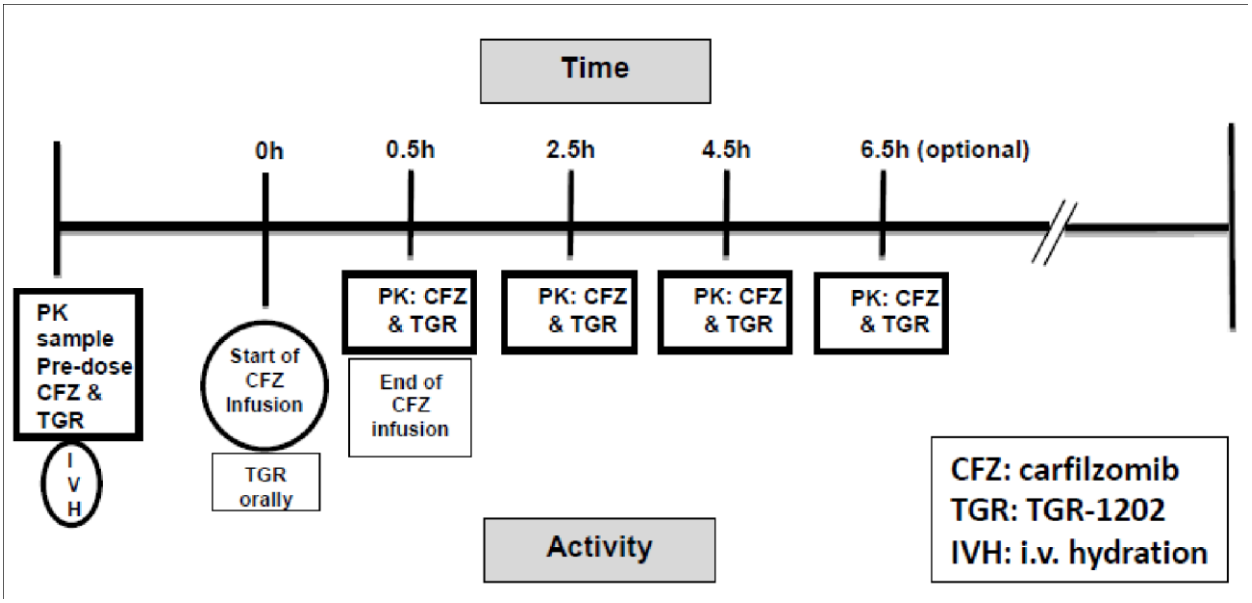
Agent Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from Appropriate parties.

9. PHARMACOKINETIC & PHARMACODYNAMIC STUDIES

9.1 PHARMACOKINETIC STUDIES

During cycle 1 day 1, blood will be collected in heparinized tubes pre- and post-treatment (Figure 3). After centrifuge, plasma will be stored in polypropylene screw top tube at -80ºC until evaluation by liquid chromatography.

Figure 3. PK Studies on Cycle 1 Day 1



9.2 PHARMACODYNAMICS STUDIES

9.2.1 BIOPSIES

The patient will have the option of checking off boxes within the main consent form for this study to indicate consent or denial for the following optional studies.

A lymph node fine needle aspiration (FNA), core-needle biopsy or bone marrow biopsy will be performed prior to therapy and/or on between day 8 and 21 of cycle 1 after TGR-1202 and carfilzomib administration. Fine needle aspirations will be performed as follows:

Fine Needle Aspirations (FNA): A series of FNAs will be performed on palpable tumors in consenting patients as a function of drug exposure. In general, at least 6 aspirations will be made using a sterile 10 cc syringe over the larger volume of the palpable tumor. Once the needle is placed into the tumor, the plunger will be withdrawn and pushed several times to obtain a sufficient sample from that location. Once withdrawn from the tumor, the syringe will be flushed clean in 1-2 mL of RPMI. This procedure will be repeated up to 6 times in one tumor, flushing the syringe needle in the same 1-2 mL of RPMI. Previous experiences in mice have established that performing fewer than 6 aspirations on any given tumor is associated with irreproducible results. Once the samples are acquired, the cells will be centrifuged, and resuspended in 1 mL of RPMI.

Correlations with the results of these studies will then be compared to the pharmacokinetic profile in order to establish the relationship with concentration, and the previous data obtained on the in vitro studies.

Tumor Tissue Biopsies: The biopsies will be performed by a surgeon if necessary, or by interventional radiology. A cytopathologist will evaluate the biopsy for tumor cells microscopically at the time of the biopsy. If multiple lymph nodes are available, the safest lymph node will be selected. The choice of FNA versus biopsy will be made based on safety, accessibility, and likelihood of being pathologic. A biopsy confirming recurrent or refractory disease is mandatory for participation in study. The second FNA or biopsy is encouraged, but is not mandatory. Tissue will be labeled only with the protocol-specific unique identifier. Correlative studies will be

performed, including staining of c-Myc, eIF4F and its upstream regulators (mTOR, 4EBP1) by IHC.

Bone Marrow Biopsy: a bone marrow aspirate and biopsy will be performed by the study team when it is clinically necessary.

9.2.2 HANDLING OF SPECIMENS

All biopsies will be snap-frozen and sent to Surgical Pathology, flagged for use in the protocol. Paraffin blocks will be made to confirm histological diagnosis, and appropriate immunohistochemical staining will be performed per standard clinical practice. Remaining tissues will be used for the pharmacodynamic analysis, including staining of c-Myc, eIF4F and its upstream regulators (mTOR, 4EBP1) by IHC.

10. STUDY CALENDAR

Baseline evaluations are to be conducted as indicated in the table below, prior to start of protocol therapy. Scans must be done <4 weeks prior to the start of therapy. 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. Table 6 describes the study calendar in details.

Table 6. Study Calendar

Cycle		Cycle 1 (28-day cycle) (±4 days)						Cycle 2+ (±4 days)						End of treatment[k]	End of Study (4 weeks after last dose)	Followup[l]
	Screening	D1		D8		D15		D1		D8		D15				
Eligibility & Safety Monitoring																
Informed Consent	X[a]															
Demographics	X[a]															
Medical History	X[a]															
EKG	X[a]	X												X		
Urinalysis	X[a]	X[e]						X								
CT (or PET/CT) [f]	X[a]												X[f]	X[f]		X[f]
Bone Marrow Biopsy	X[h]															
Lymph Node Biopsy	X[h]															
Concurrent Medications	X[b]	X[e]		X		X		X		X		X		X	X	X
Physical exam	X[b]	X[e]		X		X		X						X	X	X
Vital Signs, weight	X[b]	X		X		X		X		X		X		X	X	X
Performance Status	X[b]	X		X		X		X						X	X	X
CBC w/ differential	X[b]	X[e]		X		X		X		X		X		X	X	X
Chemistry[c]	X[b]	X[e]		X		X		X		X		X		X	X	X
Creatinine clearance	X[b]	X[e]						X								
Serum b-hCG[d]	X[b]	X						X								
Drug Administration																
Oral TGR-1202		→ D1-21						→ D1-21						→		
Carfilzomib		X		X		X		X		X		X		X		
Toxicity Assessment		X		X		X		X		X		X		X	X	X
Efficacy Measurement[f]														X[f]		X[f]
Correlative Studies																
Blood for PK		X[i]														
Blood for PD		X[j]		X[j]												

Bone Marrow Biopsy	X[h]			X[g]												
Lymph Node Biopsy	X[h]			X[g]												

a. To be done within 4 weeks of treatment start date.
b. To be done within 1 week of treatment start date. CoAgs (INR, PTT, PT) at screening only.
c. Chemistries include: sodium, potassium, chloride, bicarbonate, calcium, creatinine, magnesium, LDH and hepatic function panel.
d. For patients of childbearing age.
e. Not necessary if conducted within 72 hours of screening assessment.
f. CT scans after cycles 2, 4, and 6, then q3-6 months, until disease progression or initiation of new therapy (PET/CT is optional).
g. Optional, to be done at some point between C1D8 and C1D21.
h. Pre-treatment tumor and bone marrow biopsy is ***optional*** except when the procedures are needed to establish diagnosis. The optional biopsies will be performed on patients who consented for these optional studies.
i. PK for Carfilzomib and TGR-1202. Blood will be drawn pre-dose, 0.5 hour, 2.5h, 4.5h after the start of carfilzomib (Start of carfilzomib infusion is counted as 0h). PK at 6.5h post-carfilzomib is optional.
j. PD studies. Blood will be drawn on C1D1 pre-dose and between C1D8 and C1D21 at 4h post-treatment (same day as the optional tumor biopsy if possible).
k. To be done within 4 weeks of treatment stop date.
l. May be done +/- 5 days.

11. MEASUREMENT OF EFFECT

The primary objective of the Phase I study is to evaluate the safety and tolerability of the study drugs. The measurement of toxicity is outlined in Section 7.

The primary objective of the Phase II study is to evaluate clinical response. Patients will be reevaluated at the end of even numbered cycles. Response will be evaluated with physical exam, computerized tomography (CT) and tissue biopsies as defined by the guidelines of the International Harmonization Project Group 2007 Revised Response Criteria. [51] Positron emission tomography / computerized tomography (PET/CT) will be utilized if available (optional).

11.1 EVALUATION OF RESPONSE

For the phase I part of the study evaluable disease will be utilized as the reference for response. For the phase II part of the study measurable disease criteria will be utilized for response assessment, according to the updated Cheson Criteria/ Lugano Classification[1], details in Section 11.2.1.

11.1.1 DEFINITIONS

Evaluable for toxicity: Any patient receiving at least one dose of either drug will be evaluable for toxicity starting from Day 1 of Cycle 1.

Evaluable for objective response: Evaluable patients will have received at least two full cycles of therapy.

11.1.2 DISEASE PARAMETERS

Measurable disease: Measurable lesions are defined as those that can be accurately measured in two dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (PET/CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements will be recorded in millimeters (or decimal fractions of centimeters). Tumor volume will be recorded as the sum of the product of the diameters (SPD) of the largest predominant target lesions.

FDG avidity is based on comparison with background tissues. There is no specific SUV value that is considered a cut-off.

Non-measurable disease (evaluable disease): All other lesions (or sites of disease), including small lesions (<10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), 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 SUV avidity (High SUV lesions will be prioritized, even if not the largest lesions) and size (lesions with the largest SPD diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). An SPD for all target lesions will be calculated and reported as the baseline sum SPD. The baseline sum SPD will be used as reference by which to characterize the objective tumor response based on CT criteria.

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 or absence of each should be noted throughout follow-up.

11.1.3 METHODS FOR EVALUATION OF MEASURABLE DISEASE IN NHL

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 1 week 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 when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

CT, PET/CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction

algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US): Will not be used for disease assessment.

11.2 RESPONSE CRITERIA

11.2.1 EVALUATION OF MEASURABLE DISEASE IN NHL

Patient response will be determined according to the updated response criteria for NHL and HL (Table 7)

Table 7. Revised Criteria for Response Assessment (Cheson et al., JCO 2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
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.

11.2.2 RESPONSE DEFINITIONS

Complete Response (CR): Disappearance of all non-target lesions by PET/CT

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.2.3 EVALUATION OF BEST 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.

11.2.4 OBJECTIVE RESPONSE RATE

Objective Response Rate (ORR) = CR + PR based on evaluation of best response in each patient.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 DATA REPORTING

12.1.1 MONITORING

The Institutional Review Board (IRB) at Columbia University Medical Center will monitor this study.

12.1.2 RESPONSIBILITY FOR DATA SUBMISSION

The Study Coordinator is responsible for compiling data for all participants and for providing the data to the Principal Investigator for review.

12.2 DATA SAFETY MONITORING BOARD

The Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center's Data Safety Monitoring Board (DSMB) will oversee conduct of the study, patient safety and all interim analyses as specified in the data analysis plan. Detailed guidelines regarding the structure, function and decision-making mechanisms for the Data Safety Monitoring Board are provided in the DSMB charter.

12.3 INVESTIGATOR REPORTING RESPONSIBILITIES

The conduct of the study will comply with all FDA safety reporting requirements.

An IND is not needed for this study as both agents are commercially available.

12.4 STUDY AUDITING

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by the sponsors or their representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

12.5 PROTOCOL AMENDMENTS

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by the sponsors, including TG Therapeutics and Amgen. Amendments should only be submitted to IRB/EC after consideration of TG Therapeutics and Amgen review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

12.6 PROTOCOL DEVIATIONS

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

13. STATISTICAL CONSIDERATIONS

13.1 STUDY DESIGN/ PRIMARY ENDPOINTS

Phase I

This is an open label, single institution Phase I study using the 3+3 dose escalation design.

The primary objective is to determine the MTD, MAD, and DLT of TGR-1202 in combination with carfilzomib. The safety and toxicity of this combination will be evaluated.

All patients who receive any amount of drug will be available for toxicity. Adverse events will be graded using the NCI CTCAE v4.0.

The dose escalation scheme will follow the guideline in Section 5.

Toxicities will be described by intensity at each dose level.

Phase Ib

Phase Ib is will consist of the combination of oral TGR-1202 and carfilzomib in patients with relapsed and refractory PTCL and C-MYC positive DLBCL.

The primary objective is to evaluate the safety and toxicity of the combination of TGR-1202 and carfilzomib at the MTD dose level in patients with R/R PTCL and C-MYC positive DLBCL.

13.2 SAMPLE SIZE/ACCRUAL RATE

Phase I

An estimated 9 patients (up to a maximum of 12) with R/R HL and NHL will be accrued to the Phase I study with 3 cohorts (Tables 2 & 3). A minimum of 3 patients will be treated at each dose cohort. If no DLT is reached in cohort 3, then a total of 6 patients will be treated at that dose level.

We estimate accrual of an average of 1 patients per month, with a goal of completing a maximum of 12 accruals within 12 months.

Phase Ib

The expansion phase will accrue a total of 15 patients with PTCL or C-MYC positive DLBCL.

We estimate accrual of an average of 1-2 patients per month, with a goal of completing 15 accruals within 10 months.

13.3 ANALYSIS OF SECONDARY ENDPOINTS

Phase Ib

Secondary Objective: To estimate ORR defined as best response by 4 cycles.

Disease and patient characteristics at baseline will be summarized using descriptive statistics. For qualitative variables, frequency distributions and proportions will be provided; for quantitative variables, summary statistics (e.g., mean, median, quartiles, standard deviations, etc) and graphical displays (e.g., box plots). Overall response rates will be estimated upon completion of the study along with exact 95% confidence intervals.

14. REFERENCES

1. Cheson, B.D., et al., *Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2014. **32**(27): p. 3059-68.
2. Jemal, A., et al., *Cancer statistics, 2010.* CA Cancer J Clin. **60**(5): p. 277-300.
3. Savage, K.J., et al., *MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy.* Blood, 2009. **114**(17): p. 3533-7.
4. Barrans, S., et al., *Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab.* J Clin Oncol, 2010. **28**(20): p. 3360-5.
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