COLUMBIA UNIVERSITY MEDICAL CENTER

TITLE: **PHASE II STUDY OF THE PHOSPHOINOSITIDE-3-KINASE-DELTA INHIBITOR TGR-1202 IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA**

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PROTOCOL SYNOPSIS

Title:

Phase II Study of the Phosphoinositide-3-Kinase-Delta Inhibitor TGR-1202 in Patients with Relapsed or Refractory Follicular Lymphoma

Study Design:

This is an open label, phase II study of TGR-1202 in patients with relapsed or refractory Grade 1, 2, or 3A follicular lymphoma (FL).

The primary objective of the study is to determine the Overall Response Rate (ORR) (complete remission [CR] + partial remission [PR]) in patients with relapsed or refractory (R/R) FL.

In addition, we will determine the genetic and other novel biological markers that may be predictive of response or resistance to TGR-1202.

Objectives:

Primary Objectives

 Determine the ORR of TGR-1202 in R/R FL.

Secondary Objectives

- Determine the genetic and other novel biological markers that may be predictive of response or resistance to TGR-1202 in patients with relapsed or refractory FL.
- Describe the Progression Free Survival (PFS), Duration of Response (DoR) after treatment with TGR-1202
- Describe the number of dose delays and dose reductions and other safety profile.

Target Population

Patients with relapsed or refractory grade 1, 2, or 3A FL

Inclusion Criteria

1) Histologically proven diagnosis of grade 1, 2, or 3A FL.
2) The diagnosis of relapsed FL must have been made within the last 6 months of screening if no other treatment is given for the FL in the interim; if an interim treatment is given within the last 6 month, re-biopsy will be required even if there is already a biopsy proven relapsed FL within the last 6 months.
3) Pre-treatment biopsy must establish the diagnosis AND have enough remaining tissues to satisfy the mandatory research studies.
4) Relapse following first line immunotherapy or chemoimmunotherapy. There is no upper limit to the number of therapies received prior to study entry. Prior therapies may include high-dose therapy with autologous stem cell rescue.
5) Measurable Disease according to the Lugano classification (Cheson et al., 2014a). See Appendices 1 and 2.
6) Lymphoma that is amenable to safe pre-treatment and post-treatment biopsy. The safety of the procedures will be determined by the treating physician and the surgeon (or other proceduralist) in consultation with the PI, and in accordance with standard clinical practice. Acceptable sites of disease include, for example: (1) palpable tumor mass that is accessible under direct visualization or sonogram, (2) non-palpable tumor tissue that is accessible for biopsy under CT or sonogram guidance, (3) bone marrow.
7) Age $\geq$18 years
8) ECOG performance status $\leq$2 (see Appendix 3).
9) Patients must have adequate organ and marrow function as defined below:
    a. absolute neutrophil count $\geq$1,000/microliter
    b. platelet count $\geq$50,000/microliter
    c. bilirubin $\leq$1.5X institutional upper limit of normal
    d. aspartate transaminase (AST, SGOT)/alanine transaminase (ALT, SGPT) $\leq$3.0X institutional upper limit of normal
    e. Serum creatinine $\leq$2.0X institutional upper limit of normal or creatinine clearance $\geq$50 mL/min (according to the Cockroft and Gault equation).
10) Negative serum pregnancy test within 7 days prior to Cycle 1/Day 1 for women of childbearing potential.
11) All women of childbearing potential must agree to use an effective barrier method of contraception, as described in Appendix 4, during the treatment period and for at least 1 month after discontinuation of the study drug. Male subjects should use effective barrier method of contraception during the treatment period and for at least 1 month after discontinuation of the study drug (see Appendix 4).
12) Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

1) Grade 3B FL or evidence of transformation to a more aggressive lymphoma
2) Prior and concomitant therapy:
    a. Prior exposure to any PI3 Kinase inhibitor
    b. Exposure to chemotherapy, radiotherapy, or immunotherapy within 3 weeks prior to entering the study or lack of recovery from adverse events (AE) due to previously administered treatments.
    c. Ongoing chronic immunosuppressants (e.g. cyclosporine) or systemic steroids that have not been stabilized to the equivalent of ≤10 mg/day prednisone prior to the start of the study drug.
    d. Other concurrent investigational agents during the study period.
3) Prior allogeneic stem cell transplant
4) Central nervous system lymphoma, including lymphomatous meningitis
5) Acute intercurrent illness including, but not limited to, active infection, unstable congestive heart failure, unstable angina pectoris, psychiatric illness or any social situation that would limit compliance with study participation requirements in the judgement of the investigator.
6) Major surgery performed within 4 weeks of study entry
7) Pregnant or nursing women
8) Active concurrent malignancy (except non-invasive non-melanoma skin cancer, carcinoma in situ of the cervix, or prostate intraepithelial neoplasia). If there is a history of prior malignancy, the patient must be disease-free for ≥ 3-years at the time of study entry. 9) Documented Human Immunodeficiency Virus (HIV)-infection
10) Active hepatitis A, hepatitis B, or hepatitis C infection (see Appendix 5).
11) History of tuberculosis treatment within 2 years of study entry
12) Administration of a live vaccine within 6 weeks of first dose of study drug
13) Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
14) Prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy)
15) Lymphoma that is not amenable for mandatory pre- and C2D15 post-treatment biopsy as described in item 4) of the inclusion criteria.
16) Unstable or severe uncontrolled medical condition (e.g. unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the risk to the patient associated with his or her participation in the study
17) Clinically significant cardiovascular abnormalities such as:
    a. Angina not well-controlled by medication
    b. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of enrollment
    c. Symptomatic or documented congestive heart failure that meets New York Heart Association (NYHA) Class III to IV definitions (see Appendix 6);
    d. History of stroke within the last 6 months prior to screening

Inclusion of Women and Minorities

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

Treatment Plan

Patients will be treated with TGR-1202 at a dose of 800 mg daily from day 1 to 28 on a 28-day cycle.

Duration of Treatment

Patients will be treated until one of the following events occurs:

- Disease progression
- Unacceptable adverse event(s)
- Withdrawal of consent
- Changes in the patient's condition that render continuation of the study drug unacceptable in the judgment of the treating physician
- An event that in the judgment of the treating physician warrants discontinuation of therapy.
- Patient withheld study drug for >28 days

Sample Size

The study will accrue a total of up to approximately **20 patients**.

Safety

Patients will be monitored carefully for the development of AE. AE will be evaluated according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Efficacy Outcome

Patients will be monitored for clinical and/or radiographic evidence of disease response. Response will be evaluated using clinical parameters, CT or PET/CT scan (PET/CT scan is preferred), and bone marrow or other tissue biopsy, according to the *Updated Recommendations for Evaluation, Staging, and Response Assessment for Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.(Cheson et al., 2014b)*

Figure 1: Study Plan Flow Chart

Consent:

- Informed consent for participation in the clinical study
- Informed consent for participation in the correlative studies

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Screening:

- History, Physical examination
- Peripheral blood testing
- Tissue biopsies
- Imaging: CT scan of the neck, chest, abdomen, and pelvis (and/or PET/CT scan)

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Cycle 1:

Intervention

TGR-1202 given orally at a dose of 800 mg daily on a continuous basis. Cycle duration : 28 days

Evaluation

- Visit and laboratory evaluation of safety on Days 1, 8, 15, 22
- PK and PD studies pre-treatment on day 1 and post-treatment on days 1 and 15

↓

Subsequent Cycles:

Intervention

TGR-1202 given orally at a dose of 800 mg daily on a continuous basis. Cycle duration : 28 days

Evaluation

- Visit and laboratory evaluation of safety on Day 1
- CT scan of the neck, chest, abdomen, and pelvis (and/or PET/CT) at the end of Cycle 2 and 6. Thereafter, restaging CT scans will be repeated every 4 months, or every 6 months if a complete response is achieved.
- Bone marrow and/or other target tissue biopsy to confirm CR.
- Mandatory and optional PD studies post-treatment on cycle 2 day 15, cycle 4, day 15 and at the end of treatment and disease progression, if applicable.

↓

Discontinuation:

Treatment is continued until one of the following occurs:

- Unacceptable adverse events
- Disease progression or initiation of new therapy
- Withdrawal of consent
- Changes in the patient's condition that render further treatment unacceptable in the judgment of the treating physician.
- Any event that the judgment of the treating physician warrants discontinuation of therapy
- Patient withheld study drug for >28 days

Figure 2. Pharmacokinetics (PK) schedule

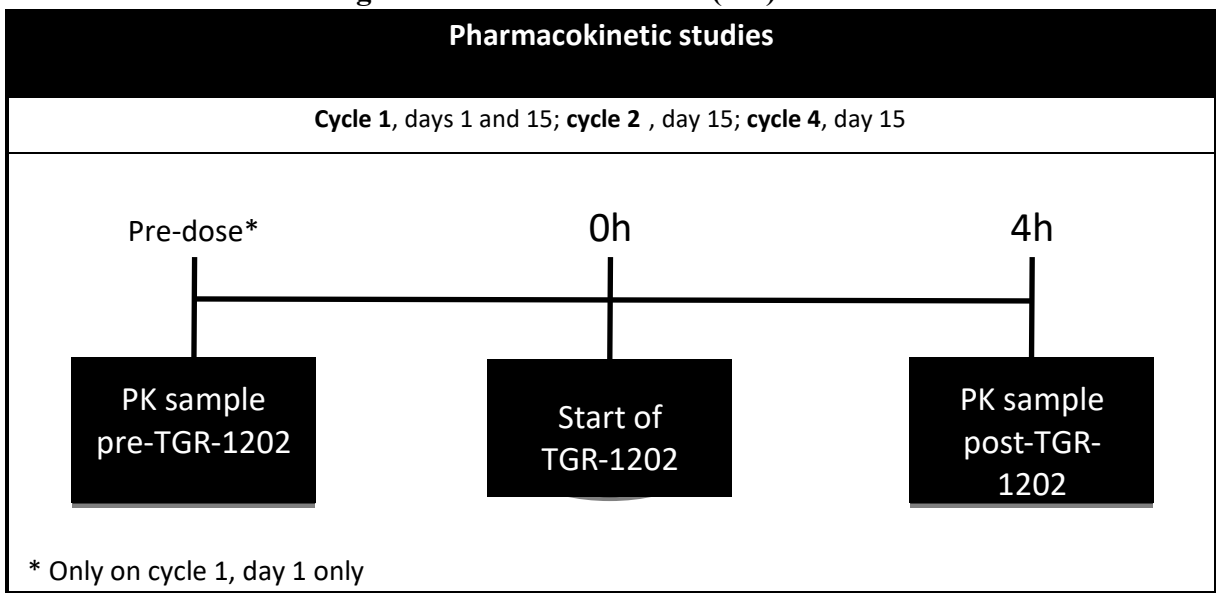
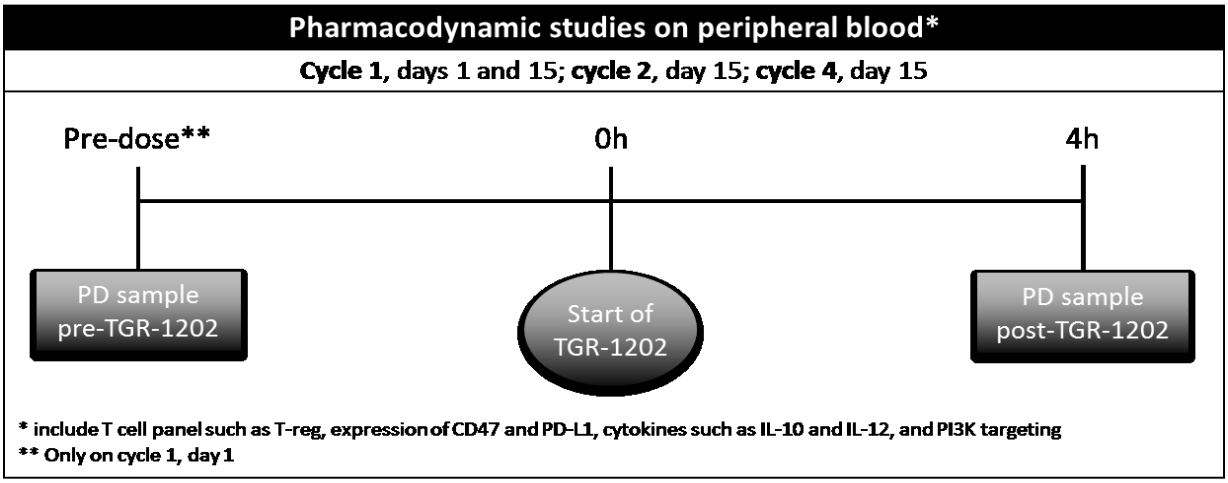


Figure 3. Pharmacodynamic (PD) Schedule



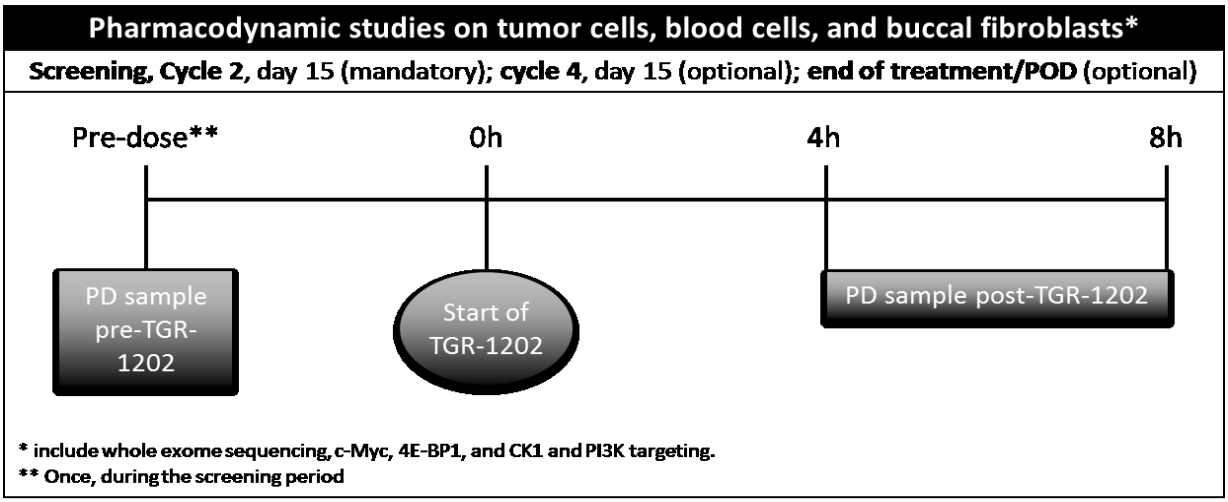
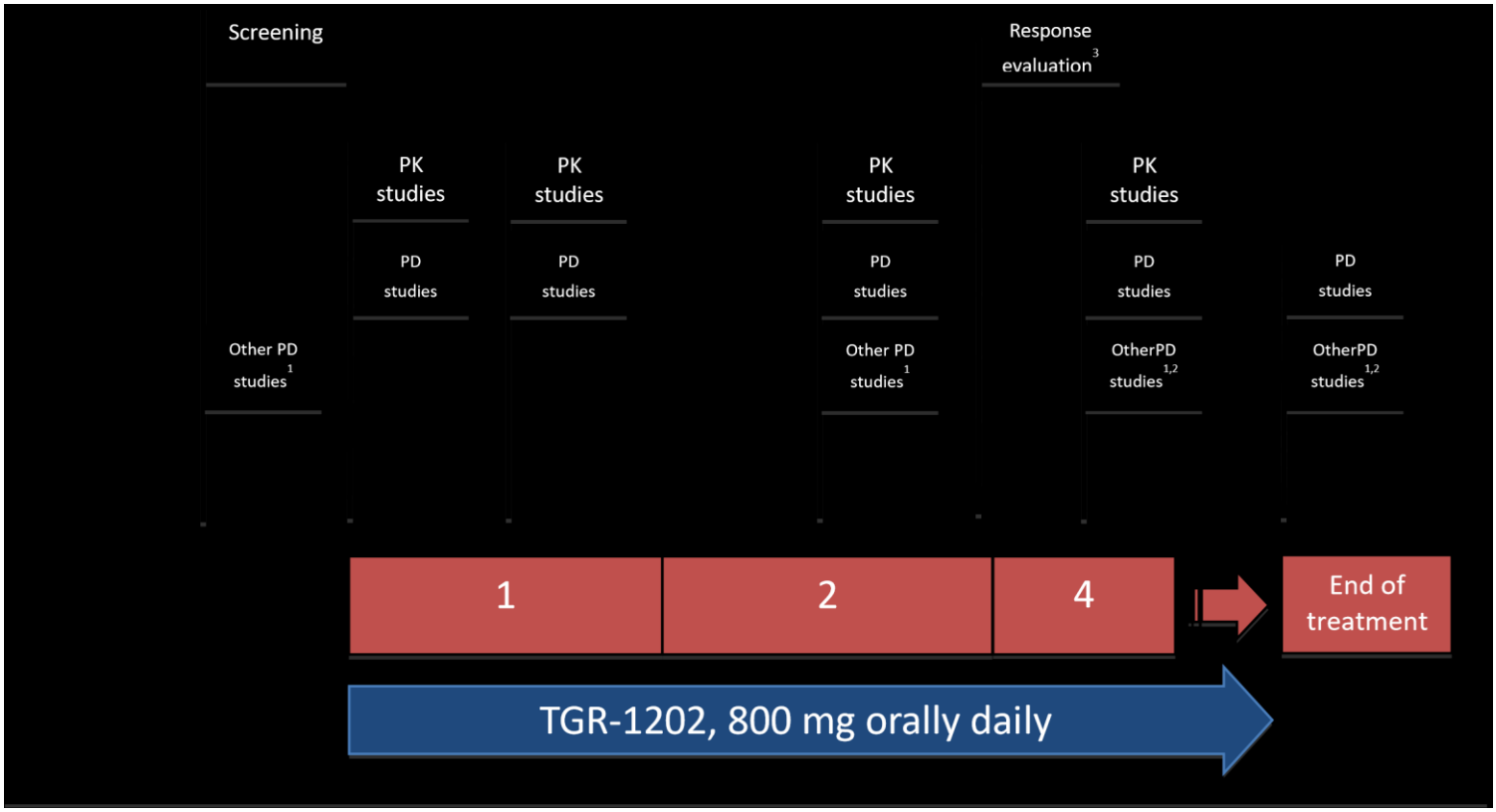


Figure 4. Study schema



[1] Includes tumor cells, blood cells, and buccal fibroblasts; tumor tissue includes nodal or extranodal tumor tissue that can be visualized and/or palpated + bone marrow aspiration and biopsy if bone marrow positive for lymphoma; [2] Optional; [3] To be performed after cycle 2 and 6, and every 3 to 6 months therea fter at the discretion of the treating physician. Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; PB, peripheral blood

<u>Note:</u> Patients who experience toxicity and require drugs to be withheld may not be candidates for biopsy. Patients who miss 4 or more doses of drug prior to a planned biopsy should be considered ineligible for biopsy, and should be replaced. The ultimate decision will be at the discretion of the treating physician.

TABLE OF CONTENTS

1. OBJECTIVES

Primary Objective

The primary objective of the study is to determine the Overall Response Rate (ORR) (complete remission [CR] + partial remission [PR]) in patients with relapsed or refractory (R/R) FL.

Secondary Objectives

Determine the genetic and other novel biological markers that are predictive of response and resistance to TGR-1202 in patients with relapsed or refractory FL.

Describe the Progression Free Survival (PFS), Duration of Response (DoR) after treatment with TGR-1202

Describe the number of dose delays and dose reductions

2. BACKGROUND

Overview of Indolent Lymphomas

The Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies with varying patterns of clinical behavior and responses to treatment (Armitage, 1993). Most NHLs are of B-cell origin. Indolent NHLs (iNHL) are a group of incurable slowgrowing diseases and represent approximately half of NHL, and are also quite heterogeneous (Arcaini et al., 2012; Sousou and Friedberg, 2010; Swerdlow et al., 2008). The major types of iNHL include FL, marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), and small lymphocytic lymphomas (SLL). The most common subtype of iNHL is FL, constituting approximately 70% of the iNHL (Bello et al., 2012; Sousou and Friedberg, 2010). MZL accounts for only 5 to 17% of all NHL in adults, while SLL constitutes approximately 6% and WM approximately 1%.

Overview of Follicular Lymphoma

FL is the most common subtype of indolent lymphoma. *BCL2* gene dysregulation caused by the t(14;18) translocation is frequently seen in FL, although it is not diagnostic of FL.(Rambaldi et al., 2002) Mutations in histone-modifying genes have recently been described and may be variably involved in its pathogenesis (Morin et al., 2011; Pasqualucci et al., 2014). FL typically follows an indolent course with a median overall survival (OS) of 7-10 years, though this may be changing rapidly with the advent of many well tolerated new drugs and new immunotherapeutic agents. Although FL initially responds well to treatment it is characterized by recurrent relapses or progression with progressively shorter intervals in between (Salles, 2007). Transformation to diffuse large B-cell lymphoma and other aggressive lymphoma occurs at a rate of approximately 2% to 3% per year (Bastion et al., 1997).

The prognosis of FL depends on the histologic grade, stage, treatment and age of the patient. The disease is considered incurable with the exception of a small minority of patients with stage 1 FL who may be curable with radiation therapy. Eventually most FL patients die of lymphoma regardless of the treatment. The Follicular Lymphoma International Prognostic Index (FLIPI)

(Solal-Celigny et al., 2004) and its revised version, FLIPI2 (Federico et al., 2009), have been developed for the assessment of newly diagnosed FL patients, but their use in relapsed FL has not yet been fully studied. Importantly, there is little to no information on risk stratification as a function of the FLIPI in this disease, though guidelines based on tumor bulk (low vs advanced) have been advanced and provide some clinical guidance on how to stratify patients.

In addition to clinical demographic parameters and prognostic indices, biological (immune signature) prognostic factors (Dave et al., 2004; Federico et al., 2009; Gribben, 2010; SolalCeligny et al., 2004) and lymphoma-mediated immunosuppression (Ramsay et al., 2009) have been noted to be common in FL, pointing to the importance of the impaired host immune response in the pathogenesis of this disease.

Treatment of Follicular Lymphoma

There is no standard treatment for patients with relapsed/refractory FL patients and the number of available treatment options is rapidly expanding. These can include watch-and-wait, depending on the burden of the disease at diagnosis or at relapse, radiation, single-agent or combination chemotherapy, rituximab monotherapy or rituximab in combination with immunomodulatory (lenalidomide) or pathway-targeted drugs (idelalisib), obinutuzumab, with or without bendamustine, rituximab containing chemotherapy regimens such as BR (bendamustine, rituximab), fludarabine plus rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone), radioimmunotherapy or autologous/allogeneic stem cell transplant in some select patients (Dreyling M1, 2014; Ghielmini et al., 2013; Zelenetz et al., 2014). In addition, the repetition of a previously applied regimen is a valid option depending on the duration of the response obtained previously.

Rituximab is approved in the US, Europe and other countries for treatment of relapsed or refractory FL as a single agent and is extensively used in the treatment of FL as monotherapy or in combination with chemotherapy. Several studies have demonstrated the efficacy and safety of rituximab monotherapy in relapsed/refractory FL or other low-grade NHL patients, and three multicenter single-arm studies have led to regulatory approval in the US, Europe and other countries. In the first study 166 relapsed/refractory FL patients were treated with 375 mg/m^2 of rituximab weekly for 4 doses. Results demonstrated a 48% overall response rate (ORR) with 6% CR and median duration of response of 11.2 months (McLaughlin et al., 1998). In the second study, 37 relapsed/refractory low-grade NHL patients received an additional 4 weekly doses of rituximab for a total of 8 doses, resulting in increased ORR of 57% and CR of 14% (Piro et al., 1999). The third study demonstrated that the retreatment of 60 relapsed/ refractory patients who had clinical response to prior rituximab treatment with 4 weekly doses of rituximab resulted in ORR of 38% and CR of 10% (Davis et al., 2000a). Thus, in some countries, the approved number of rituximab doses is four to eight. A recent update of the results from the SAKK 35/98 trial evaluating prolonged single-agent rituximab (Martinelli et al., 2010) in relapsed/refractory FL patients treated with 4 weekly doses of rituximab followed by additional 4 maintenance doses every 2 months reported a durable response with 35% of responders still in remission at 8 years. In a Phase 2 study to evaluate the safety and efficacy of rituximab in patients with bulky relapsed or refractory low-grade or FL (Davis et al., 1999), the ORR was 43% with a median TTP of 8.1 months and median DoR of 5.9 months. The average decrease in lesion size in patients who achieved a partial response was 76%, and patients with stable disease had a decrease in average lesion size of 26%.

The importance of rituximab has also been demonstrated in clinical trials that evaluated the addition of rituximab to combination chemotherapy and as a maintenance agent after chemotherapy in patients with relapsed FL. Forstpointner et al (Forstpointner et al., 2004) reported the results from a Phase 2 randomized study evaluating R-FCM versus FCM (fludarabine, cyclophosphamide, mitoxantrone) in FL (N = 93) and MCL (N = 40) patients showing improved response rate (79% versus 58%, respectively) and median PFS (16 months versus 13 months, respectively) in R-FCM group compared to FCM. Van Oers (van Oers et al., 2010) evaluated the role of rituximab (R) both in remission induction and maintenance treatment of relapsed/refractory FL; patients were randomized to induction with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or R-CHOP, and those in complete or partial remission were randomized to maintenance or observation. The median PFS from first randomization was 20.2 months after CHOP versus 33.1 months after R-CHOP (hazard ratio [HR], 0.65; $P < .001$). Rituximab maintenance yielded a median PFS from second randomization of 51.5 months versus 14.9 months with observation. A randomized Phase 3 trial (RESORT) comparing two different rituximab dosing strategies (rituximab continuous maintenance until treatment failure RM, or rituximab re-treatment at progression, RR) for untreated, low tumor burden (LTB) FL was not able to demonstrate differences in time to treatment failure (TTF) (Kahl et al., 2014a). The mean number of rituximab doses per patient (including the 4 induction doses) was 15.8 (range 5– 31) for MR and 4.5 (range 4–16) for RR. The time to initiation of cytotoxic therapy was delayed in both arms compared to historical watch and wait strategies. Rituximab re-treatment at progression produces outcomes comparable to MR in this patient population.

The combination of rituximab and bendamustine, an alkylating agent, is approved in US, Europe and many other countries for the treatment of rituximab-refractory iNHL and showed a response rate of 90% and median PFS of 2 years in relapsed/refractory iNHL and MCL in single-arm Phase 2 studies (Robinson et al., 2008; Rummel et al., 2005). Major reported toxicities of bendamustine were myelosuppression (Grade 3 or 4 neutropenia and thrombocytopenia), nausea, infection, and fatigue. The two anti-CD20 radioimmunotherapy agents, yttrium Y90 ibritumomab tiuxetan and iodine I131 tositumomab, have demonstrated high activity in patients relapsed/refractory to chemotherapy or rituximab. Patients achieved a response rate of 60% to 80% but with significant toxicities including prolonged myelosuppression with potential risk of treatment-associated myelodysplastic syndrome (MDS) and acute myelogenous leukemia (Cheson, 2003). A randomized Phase 3 trial comparing yttrium Y90 ibritumomab tiuxetan to rituximab in relapsed indolent NHL demonstrated significantly higher ORR (80% versus 56%) and CR rate (30% versus 16%) but with no significant differences in median time to progression (11.2 months versus 10.1 months) (Witzig et al., 2002).

More recently, efforts have been made to find novel regimens for the treatment of relapsed FL that do not contain non-specific cytotoxic agents. Such efforts include combinations of rituximab with a second monoclonal antibody, such as anti-CD80 galiximab (Czuczman et al., 2012; Czuczman et al., 2005) and anti-CD22 epratuzumab (Leonard et al., 2005), and with targeted agents such as bortezomib (Baiocchi et al., 2011) interferon (Davis et al., 2000b; Sacchi et al., 2001), cytokines granulocyte macrophage colony stimulating factor (GM-CSF) (Cartron et al., 2008) and IL-12 (Ansell et al., 2002), as well as lenalidomide.(Witzig et al., 2015) Of these combinations, a Phase 3 study comparing bortezomib plus rituximab versus rituximab single agent has been reported. In this study 676 rituximab-naïve or rituximab-sensitive patients with relapsed Grade 1 or 2 FL were randomly assigned in 1:1 ratio to receive rituximab alone (weekly during first cycle x 4 doses and

then on Day 1 of cycles 2 to 5) or in combination with bortezomib (weekly x 4 doses of cycles 1 to 5). While the difference in the PFS was statistically significant (p = 0.039), the magnitude of the difference in the median PFS was < 2 months (11.0 months in the rituximab-only arm and 12.8 months in the rituximab-bortezomib arm).

PI3K, PI3K-δ and PI3K-γ Inhibition

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 synthesis 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 and is known to play a role in insulin signaling and glucose homeostasis (Knight et al., 2006; Vanhaesebroeck et al., 2010). 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 the treatment of 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])(FungLeung, 2011).

PI3K-□ and PI3K-□ are expressed in hematopoietic cells, and are critical for the ability of normal immune cells to respond to survival and differentiation signals in their environment. In cancer cells, where the pathways mediated by PI3K-δ and -γ contribute to survival, proliferation, and differentiation, the use of PI3K inhibitors has a stronger therapeutic rationale. The tumor microenvironment plays an important role in the development and maintenance of cancer (Hanahan and Weinberg, 2011). Through the expression of various cytokines, growth factors, and chemokines, tumor cells recruit other cell types, including myeloid cells capable of differentiating into tumor-associated macrophages (TAMs) which promote angiogenesis and augment tumor growth (Lewis and Pollard, 2006). Therefore, agents that target TAMs as well as other types of infiltrating leukocytes are of potential therapeutic interest across most of oncology. Recently, the work of Schmid et al. demonstrated that tumor growth, invasion of $CD11b^{+}$ myeloid cells, angiogenesis and metastasis of tumors implanted into PI3K-γ deficient mice were substantially suppressed compared to wild-type controls and treatment of mice bearing Lewis Lung Carcinoma (LLC) allografts with the selective PI3K-γ inhibitor TG100-115, suppressed tumor inflammation, growth and angiogenesis despite having no effect on LLC proliferation in vitro (Schmid et al., 2011).

In hematological malignancies including acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL), over-expression and constitutive activation of PI3K-δ suggests that PI3K-δ inhibition could have therapeutic benefit (Billottet et al., 2009; Billottet et al., 2006; Herman et al., 2010; Herman et al., 2011; Ikeda et al., 2010; Meadows et al.,

2010). The PI3K- isoform specific inhibitor idelalisib (formerly known as CAL-101/GS1101) has demonstrated clinical activity in patients with hematologic malignancies (Flinn et al., 2014) and was approved by the FDA in 2014 for the treatment of CLL and FL (Furman et al., 2014a; Gopal et al., 2014a). 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 MCL and other refractory NHL (Flinn et al., 2014; Hoellenriegel et al., 2011; Kahl et al., 2014b; Lannutti et al., 2011; Meadows et al., 2010; Webb et al., 2010). In refractory or relapsed iNHL and in CLL patients, CAL-101 has been combined with BR demonstrating robust clinical activity (Flinn et al., 2010; Sharman et al., 2011). Subsequently, two other PI3K inhibitors, including copanlisib and duvelisib, demonstrated similar clinical activity in FL and were approved by the FDA in 2017 and 2018, respectively, for the treatment of FL. However, these drugs have serious and fatal toxicities.

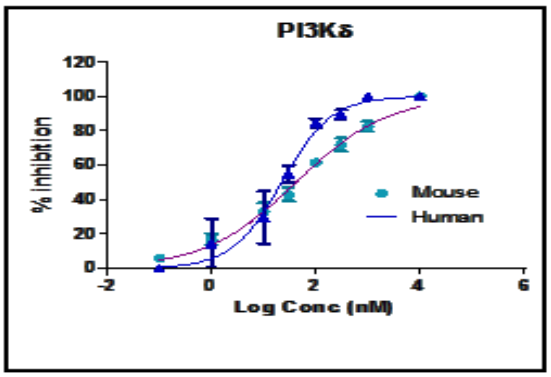
The established roles of PI3K in cancer cells, and in the biology of the tumor microenvironment, support the development of PI3K-δ inhibitors in patients with hematological malignancies, in particular lymphoproliferative disorders, either as single agents or in combination with other drugs.

TGR-1202

TGR-1202 is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K.(Friedman et al., 2014) TGR-1202 is currently in a Phase I dose escalation trial and has been administered safely at daily doses up through 1200 mg QD.

Pre-clinical development of TGR-1202

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) (11). Selectivity over the other three isoforms, namely, α, β, and γ was also determined (Prasanna R, 2011) (Seeta N, AKT phosphorylation in THP-1 cells. Study Report IVT-5264-ATP-08, 2011) (Seeta N, AKT phosphorylation in MOLT-4 cells. June Study Report IVT-5264-APM-10, 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.



TGR-1202 potency against human and mouse PI3K isoforms

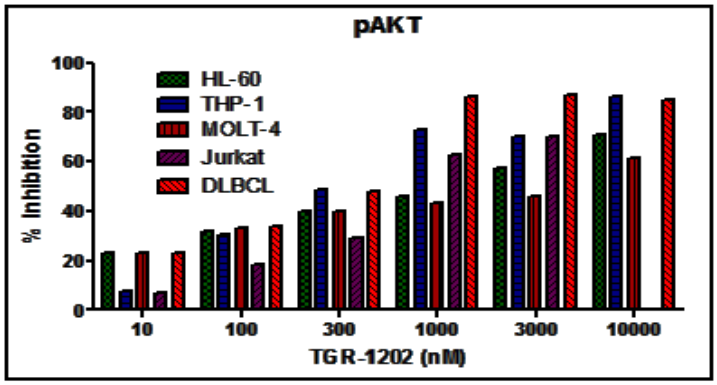
PI3K isoforms (Human)	IC_{50} (nM)
α	>10,000
β	1,116
γ	1,065
δ	22.23

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 (17). Cells were incubated with TGR-1202 for different timeperiods (72 -96 h) based on their doubling time. Data demonstrated the ability of TGR-1202 to inhibit leukemic cell proliferation albeit with different potencies based on the cell type.

Overall, a 50% growth inhibition for majority of B, T, and monocytic cell lines was achieved at a concentration between 0.5 and 7.5 µM of TGR-1202.

Subsequent to cell viability, the effect of TGR-1202 on AKT phosphorylation (12, 13, 14, 15, 16) 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.

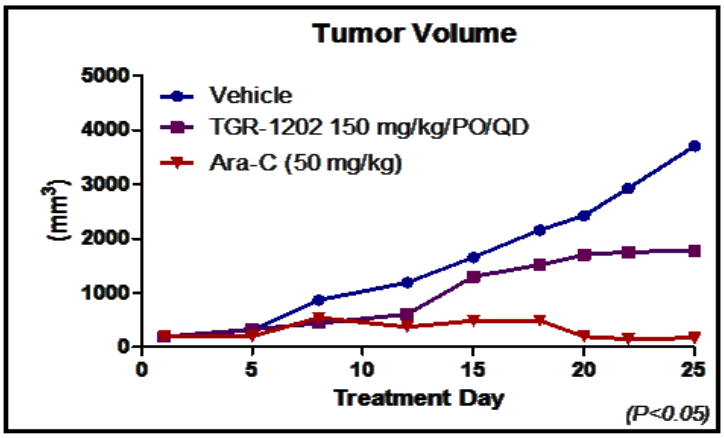
Reduction of pAKT by TGR-1202 in cell lines by Western blotting



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.

TGR-1202 In vivo efficacy



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

Once daily oral administration of TGR-1202 was tolerated in mice at free base dose levels of 50 and 150 mg/kg/day. Increases in liver weights, microscopic findings in the liver and the increases in serum cholesterol, and female only ALT, AST, and GGT levels were observed at 750 mg/kg/day of free base (the highest dose tested) and were considered adverse. The noobserved-adverse-effect level (NOAEL) was considered to be 150 mg/kg/day in mice.

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

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

Clinical development of TGR-1202

Single-agent activity in patients with relapsed or refractory hematologic malignancies.

TGR-1202 is under evaluation in an ongoing single-agent Phase I dose-escalation study in patients with relapsed and refractory hematologic malignancies (O'Connor et al., 2015).

Patients were enrolled in a 3+3 dose-escalation design starting at 50 mg QD with subsequent cohorts evaluating doses as high as 1800 mg QD. In an effort to further improve the oral bioavailability of TGR-1202, the particle size of the drug product was reduced through a micronization process, resulting in greater absorption when tested in a bioequivalence crossover study in healthy subjects (see Section Healthy Subject Pharmacokinetics below). This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1200 mg QD, with no maximum tolerated dose (MTD) reached. Intra-patient dose escalation rules have allowed patients enrolled into the study in early cohorts to increase their dose of TGR1202 as subsequent higher cohorts have cleared safety evaluation.

As of August 2015, 75 pts were evaluable for safety including pts with CLL, FL, Hodgkin's (HL), DLBCL, MCL, and MZL. Patients had a median age of 65 yo (range: 22-85), 67% male, ECOG 0/1/2: 26/47/2, median prior Tx: 3 (range: 1-14), and 49% refractory to prior Tx. No Gr≥3 AEs were observed in ≥10% of pts. AEs (all grades, all causality) in >20% of pts were limited to nausea (44%, Gr3/4 0%), diarrhea (36%, Gr3/4 1%), and fatigue (31%, Gr3/4 3%). Notably, general tolerability and the incidence of hepatotoxicity and colitis appear significantly less than that reported with other agents in this class. Expansion cohorts are open at 800 mg, 1000 mg, and 1200 mg QD. Of 16 evaluable CLL pts, 15 (94%) achieved a nodal PR (median nodal ↓ of 76%), of which 10 (63%) achieved a PR per Hallek 2008 criteria. Among the 32 evaluable NHL patients, 10 achieved an objective response, including 3/11 evaluable patients with DLBCL, while responses have been limited in pts with MCL (1/5) and HL (1/9). Of the 16 evaluable indolent NHL (FL & MZL) pts, 14 (88%) have achieved reductions in tumor burden with 6 pts on study for over 12 cycles (and durations upwards of 29+ cycles), with 5/12 FL and 1/4 MZL pts achieving an objective response to date. Notably, a strong exposure-response relationship has been observed. Of the 24 patients starting TGR-1202 at 800 mg or 1200 mg of the micronized formulation, 19 (79%) remain on therapy, with 9/18 (50%) evaluable pts (6 too early to evaluate) achieving an objective response to date (range on study 3 - 49+ weeks).

A dose-dependent response has been observed with TGR-1202, with a dose of 800 mg or higher of the initial formulation or any dose of the micronized formulation producing significant nodal reductions among CLL patients. AEs observed included diarrhea, nausea, fatigue, cough, anorexia, headache, vomiting, rash, neutropenia, constipation, dyspnea, and thrombocytopenia. See the comprehensive Adverse Events and Potential Risks Lists (CAEPRs) section for a complete overview of the TGR-1202 side effect profile.

Dosing of TGR-1202 initially occurred in the fasting state, but was transitioned mid-study to fed state dosing, with patients instructed to take TGR-1202 with food. All dosing of TGR-1202 is now conducted using the micronized formulation and in the fed state.

Overall, the available data on TGR-1202 suggest that it is considerably better tolerated that idelalisib and duvelisib, and does not appear to be associated with the "autoimmune-like" side effects of the other two agents in the class, including colitis and pneumonitis. In addition, the incidence of transaminitis, diarrhea and drug discontinuation is substantially lower. The clinical activity and favorable toxicity profile of TGR-1202 were published in April 2018 (Lancet Oncol. 2018 Apr;19(4):486-496. PMID: 29475723).

Healthy subject pharmacokinetic studies.

In parallel with the Phase 1 single-arm, dose-escalation study in patients with relapsed or refractory hematologic malignancies; two healthy subject, crossover, bioequivalence pharmacokinetics studies have been completed. The first pharmacokinetic study was a Phase 1 drug-food interaction study with a single 200 mg oral dose of TGR-1202 in healthy volunteers followed by a second single dose Phase 1 pharmacokinetic study evaluating the absorption, distribution, metabolism and excretion characteristics of two different oral formulations of 200 mg TGR-1202 (original formulation vs. micronized formulation) in healthy volunteers.

TGR-1202-PK101: Food Effect.

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

The statistical comparisons of TGR-1202 pharmacokinetic parameters under fasted and fed condition are shown below.

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

Food increased both the extent and rate of exposure of TGR-1202. The extent ($AUC_{0\text{-}t}$) and total extent ($AUC_{0\text{-}inf}$) of exposure increased by 61% and 67%, respectively, when TGR-1202 was administered under fed conditions compared to fasting conditions. The peak plasma levels of TGR-1202 increased by over 173% when TGR-1202 was administered with food.

Using these mean values, a 334 mg oral dose of TGR-1202 under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of TGR-1202 under fed conditions in terms of exposure based on $AUC_{0\text{-}inf}$.

TGR-1202-PK102: Formulation Effect.

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

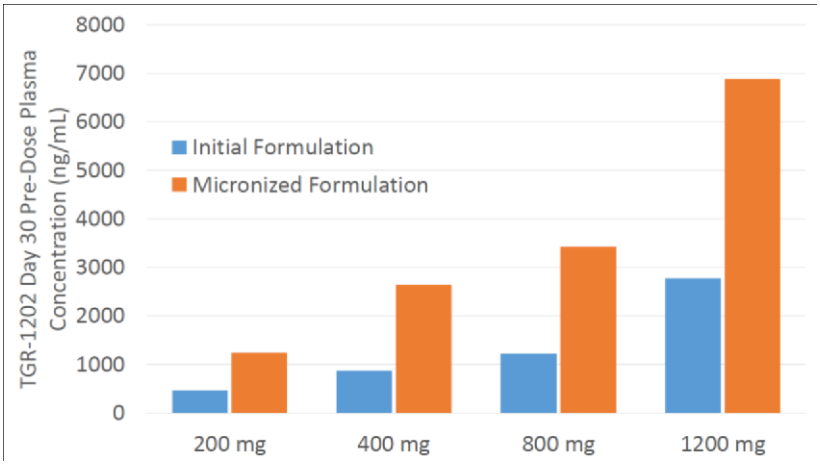
The statistical comparison of the micronized 200 mg drug product formulation versus the original 200 mg drug product formulation are shown below:

Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Original Formulation	Micronized Formulation		
$AUC_{0\text{-}t}$ (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95
$AUC_{0\text{-}inf}$ (ng·hr/mL)	7715.67	12378.19	160.43	146.49 – 175.70
C_{max} (ng/mL)	166.20	371.70	223.65	202.33 – 247.20

The micronized drug product formulation increased both the extent and rate of exposure of TGR1202 under fasted conditions. The extent ($AUC_{0\text{-}t}$) and total extent ($AUC_{0\text{-}inf}$) of exposure both increased by 60%, respectively, following administration of the modified drug product formulation relative to original drug product formulation. The Peak plasma (C_{max}) levels of TGR-1202 increased by over 124% following administration of the micronized drug product formulation relative to original drug product formulation under fasted conditions.

Using these mean values, a 320 mg oral dose of TGR-1202 in the original formulation under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of the original formulation TGR-1202 under fasted conditions in term of exposure based on $AUC_{0\text{-}inf}$.

The improved exposure seen with the micronized formulation of TGR-1202 was confirmed in patients in the Phase 1 dose escalation as well. The chart below illustrates the pre-dose plasma concentrations of TGR-1202 on Day 1 of Cycle 2 in patients administered equivalent doses of either the initial formulation in the fasting state or the micronized formulation in the fed state:



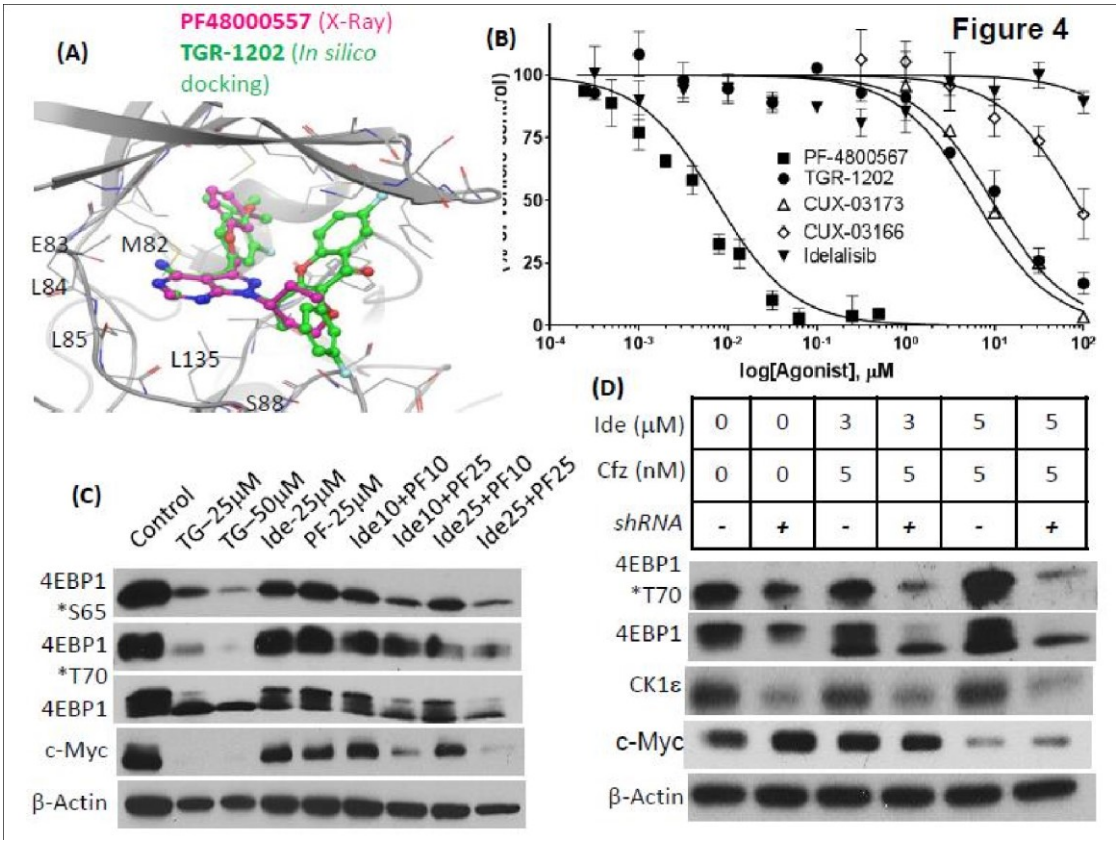
Rationale for the Study

PI3K-□ and PI3K-□ are expressed in hematopoietic cells, and are critical for the ability of normal immune cells to respond to survival and differentiation signals in their environment. In cancer cells, the pathways mediated by PI3K-δ,γ are critical for cell survival and proliferation, as well as the inductive tumor microenvironment. PI3K inhibition with idelalisib has proven successful in the treatment of patients with relapsed or refractory indolent NHL, including FL (Gopal et al., 2014a). Longer-term data of previous trials and the results of ongoing studies of idelalisib in patients with CLL or NHL have suggested that safety concerns may limit further clinical development of idelalisib in this setting. In fact, In March 2016 The U.S. Food and Drug Administration issued an alert to health care professionals about reports of an increased rate of adverse events, including deaths, in clinical trials with idelalisib in combination with other drugs. In addition six clinical trials in patients with CLL and iNHL were halted. The FDA label of idelalisib currently contains a black box warning on fatal and serious hepatitis, pneumonitis, severe diarrhea, colitis, and intestinal perforation.

Although targeting of PI3K-□ has been validated as a therapeutic strategy in lymphoma, as demonstrated by the approval of idelalisib, this strategy has several limitations. (a) Idelalisib does not have activity in aggressive lymphoma such as the most common subtype, diffuse large B cell lymphoma. (b) The PFS for idelalisib in CLL and FL is short, 5.5 and 11 months, respectively (Furman et al., 2014b; Gopal et al., 2014b). Resistance develops for essentially all patients. The mechanism of resistance is unknown, but could be due to genetic mutations, or activation of pro-survival pathways. (c) Idelalisib is associated with a very high frequency of diarrhea. Interestingly, TGR-1202 appears to have a number of features distinct from idelalisib.

Notably, TGR-1202 possesses a central pyrazolopyrimidine amine moiety that has been found to confer an ability to target a poorly understood kinase, CK1 epsilon (Blood. 2017 Jan 5;129(1):88-99. PMID: 27784673). There is emerging evidence that targeting of CK1 epsilon by TGR-1202 makes it uniquely active in silencing the translation of c-Myc through inhibiting phosphorylation of 4E-BP1 (**Figure 4**) in diffuse large B cell lymphoma (DLBCL) with overexpression of c-Myc.

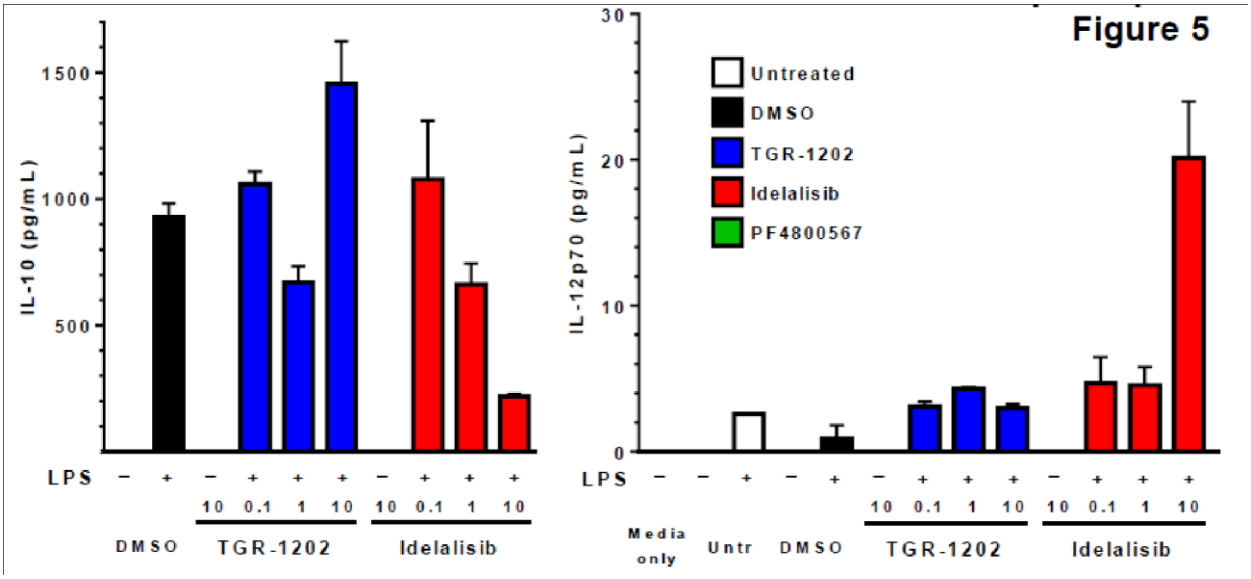
In agreement, TGR-1202 as a single agent is reported to produce a partial response in 2 of 12 patients with DLBCL.



TGR-1202 is active against CK1□. (A) Comparison of the co-crystallization of PF-4800567 and CK1ε to *in silico* docking of TGR-1202 in the active site binding pocket. **(B)** Cell-free kinase activity assay of CK1ε measuring dose (-X)-activity (-Y) curves of PF-4800567, TGR-1202, Idelalisib, CUX-03173, and CUX-03166. **(C)** Western blot analysis of LY7 cells treated by various singles agents and combinations for 24h. The numbers in the combinations indicated the drug concentrations incells stably expressing the CK1ε targeting shRNA (shRNA+) or the parental untransduced control cells (shRNA □M. **(D)** Effects of CK1ε knockdown on the combination of Ide+Cfz. LY7 -) were treated as indicated for 24h and assessed by Western blot.

It has been shown that severe diarrhea associated with idelalisib is due to erosive colitis characterized by sloughing of the luminal epithelium and exudate, numerous apoptotic bodies. intraepithelial lymphocytes, and crypt abscesses (Louie et al., 2015; Weidner et al., 2015). The pathologic findings were also observed in the kinase dead (PI3K p110dD910A/D910A) transgenic mice (Okkenhaug et al., 2002; Uno et al., 2010). The cytokines IL-10 and IL-12 have been shown to promote mucosal homeostasis and inflammation, respectively (Sartor, 2010; Uno et al., 2010). It was reported that mutant macrophages with an inactive PI3K□ (p110δKD) were associated with decreased IL-10 expression and increased IL-12 expression, a cytokine profile that was closely mirrored by the treatment of wild type macrophages with IC87114, a PI3K□ inhibitor structurally related to idelalisib (Steinbach et al., 2014). We confirmed that idelalisib caused decreased

production of IL-10 and increased production of IL-12 by macrophages stimulated with lipopolysaccharide (LPS) (**Figure 5**). Interestingly, TGR-1202 generated an opposite pattern of cytokines produced by macrophages, with increased IL-10 and decreased IL12. Collectively these results suggest that TGR-1202 may be equipped with a unique ability to generate a profile of IL-10/IL-12 that is not harmful to colonic mucosal homeostasis, opposite to the effect of idelalisib. Furthermore, this unique feature of TGR-1202 is likely related to the activity of TGR-1202 in targeting CK1δ, as shown in Figure 4.



Effects of PI3K inhibitors on IL-10/IL-12. PBMC cells from healthy donors were incubated with monocyte conditioned medium (MCM) to allow differentiation into microphages. Microphages were pretreated with the indicated drugs for 1h, then stimulated with lipopolysaccharide (LPS) for 24h and analyzed for IL-10 and IL-12.

Hypothesis: We hypothesize that if TGR-1202 acts through targeting PI3Kδ and CK1δ, then its response in patients may be associated with, and potentially predicted by, inhibition of key effectors downstream of PI3Kδ and CK1δ, including 4E-BP1, p70S6K, c-Myc, E2F1, global mRNA translation, expression of c-Myc target genes such LDHA and E2F1, and expression of PD-L1 and CD47. Conversely, resistance may be associated with mutations in the PI3Kδ and CK1δ pathways, and loss of inhibition of the above effectors. Furthermore, TGR-1202 may cause increased IL-10 and decreased IL-12 produced by macrophages.

One of the important goals of this phase II study is to discover novel genetic, biochemical, and immunological markers that are associated with the response and safety of TGR-1202 in patients with follicular lymphoma. To achieve this goal we will combine our expertise in genetics and genomics, molecular pathways, targeted therapy, immune therapeutics, and innovative animal

models to conduct extensive correlative studies using patient samples, including matched pre- and post-treatment normal and tumor tissues.

3. PATIENT SELECTION

Inclusion Criteria

1. Histologically proven diagnosis of grade 1, 2, or 3A FL
2. The diagnosis of relapsed FL must have been made within the last 6 months of screening if no other treatment is given for the FL in the interim; if an interim treatment is given within the last 6 month, re-biopsy will be required even if there is already a biopsy proven relapsed FL within the last 6 months.
3. Pre-treatment biopsy must establish the diagnosis AND have enough remaining tissues to satisfy the mandatory research studies.
4. Relapse following first line immunotherapy or chemoimmunotherapy. There is no upper limit to the number of therapies received prior to study entry. Prior therapies may include high-dose therapy with autologous stem cell rescue.
5. Measurable disease according to the Lugano classification (Cheson et al., 2014a). See Appendices 1 and 2.
6. Lymphoma that is amenable to safe pre-treatment and post-treatment biopsy. The safety of the procedures will be determined by the treating physician and the surgeon or other proceduralist, in consultation with the PI, and in accordance with standard clinical practice. Acceptable sites of disease include, for example: (1) palpable tumor mass that is accessible under direct visualization or sonogram, (2) non-palpable tumor tissue that is accessible for biopsy under CT or sonogram guidance, (3) bone marrow.
7. Age $\geq$18 years.
8. ECOG performance status $\leq$2 (see Appendix 3)
9. Patients must have adequate organ and marrow function as defined below:
    a. absolute neutrophil count $\geq$1,000/microliter
    b. platelet count $\geq$50,000/microliter
    c. bilirubin $\leq$1.5X institutional upper limit of normal
    d. aspartate transaminase (AST, SGOT)/alanine transaminase (ALT, SGPT) $\leq$3.0X institutional upper limit of normal
    e. Serum creatinine $\leq$2.0X institutional upper limit of normal or creatinine clearance $\geq$50 mL/min (according to the Cockroft and Gault equation).
10. Negative serum pregnancy test within 7 days prior to Cycle 1/Day 1 for women of childbearing potential
11. All women of childbearing potential must agree to use an effective barrier method of contraception, as described in Appendix 4, during the treatment period and for at least 1 month after discontinuation of the study drug. Male subjects should use effective barrier method of contraception during the treatment period and for at least 1 month after discontinuation of the study drug (see Appendix 4).
12. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

1. Grade 3B FL or evidence of transformation of FL to a more aggressive lymphoma 2.
Prior and concomitant therapy:
    a. Prior exposure to any PI3 Kinase inhibitor
    b. Exposure to chemotherapy, radiotherapy, or immunotherapy within 3 weeks prior to entering the study or lack of recovery from adverse events due to previously administered treatments.
    c. Ongoing chronic pharmacologic immunosuppression, e.g. cyclosporine, or systemic steroids that have not been stabilized to the equivalent of ≤10 mg/day prednisone prior to the start of the study drug.
    d. Other concurrent investigational agents during the study period.
3. Prior allogeneic stem cell transplant
4. Central nervous system lymphoma, including lymphomatous meningitis
5. Acute intercurrent illness including, but not limited to, active infection, unstable congestive heart failure, unstable angina pectoris, psychiatric illness or any social situation that would limit compliance with study participation requirements in the judgement of the investigator
6. Major surgery performed within 4 weeks of study entry
7. Pregnant or nursing women
8. Active concurrent malignancy (except non-invasive non-melanoma skin cancer, carcinoma in situ of the cervix, or prostate intraepithelial neoplasia). If there is a history of prior malignancy, the patient must be disease-free for ≥ 3-years at the time of study entry. 9. Documented Human Immunodeficiency Virus (HIV)-infection
10. Active hepatitis A, hepatitis B, or hepatitis C infection (see Appendix 5).
11. History of tuberculosis treatment within 2 years of study entry
12. Administration of a live vaccine within 6 weeks of first dose of study drug
13. Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
14. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy)
15. Lymphoma that is not amenable for mandatory pre- and C2D15 post-treatment biopsy as described in item 6) of the inclusion criteria.
16. Unstable or severe uncontrolled medical condition (e.g. unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the risk to the patient associated with his or her participation in the study
17. Clinically significant cardiovascular abnormalities such as:
    a. Angina not well-controlled by medication
    b. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of enrollment
    c. Symptomatic or documented congestive heart failure that meets New York Heart Association (NYHA) Class III to IV definitions (see Appendix 6);
    d. History of stroke within the last 6 months prior to screening

Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

General Guidelines

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

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

Study Informed Consent

Study personnel must obtain informed consent from each potential patient prior to entering the clinical study. Consent must be documented on the IRB approved consent form by obtaining the signature and date of both the patient and the investigator conducting the consent discussion.

If the patient is able to understand and willing to, but unable sign the consent form, then oral consent, attested to by the dated signature of an impartial witness (i.e., a person not involved with the conduct of the study), is the required alternative.

If the patient is unable to read, 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).

The information from the consent form should be translated and communicated to the subject in a language understandable to the subject. Consent forms will be available in English and Spanish. If the study participant is a non-English and non-Spanish speaker, the consent form must be read accurately in its entirety by a qualified professional translator. The translator must also translate all the questions the patient might have and all the answers the patient receives from the study personnel conducting the consent discussion. 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 understands the information therein and consents to participate in the study. The professional translator will sign the consent form as an impartial witness.

A copy of the consent form signed and dated should be provided to the patient before study entry.

Tests performed within 29 days prior to the date of written informed consent may be accepted as study screening tests provided that these are considered part of standard care.

The initial informed consent form and all subsequent revised written informed consent forms, as well as any amendment or additional written information regarding the study is contingent on the IRB approval. The patient or his/her legally accepted representative will be informed in a timely manner if new information becomes available that may affect the patient's willingness or ability to continue to participate in the trial. The communication of this information will be documented.

Consent for and Use of Tissue Specimens for Correlative Studies

Participation in correlative studies is mandatory for all patients. In addition to the mandatory correlative studies for all patients, there will also be optional correlative studies, which will be performed under a separate section of the informed consent procedure.

Mandatory correlative studies include the following:

 For PK studies:

1. Collection of blood at Pre-treatment.
2. Collection of blood at 4h post-treatment on C1D1, C1D15, C2D15 and C4D15.

 For PD studies:

1. Collection of blood at Pre-Treatment (total approx.3ml).
   Collection of blood at 4h post-treatment on C1D1, C1D15, C2D15 and C4D15 (total approx. 12ml).
   The studies will include T cell panel such as T-reg, expression of CD47 and PD-L1, cytokines such as IL-10 and IL-12, and PI3K targeting.
2. Collection of tumor tissues, blood cells, and buccal fibroblasts pre-treatment and 4-8h post-treatment on C2D15.
   The studies will include whole exome sequencing, and the levels/activity of c-Myc, 4E-BP1, CK1, and PI3K.

Optional correlative studies are listed below:

Collection of tumor tissues and buccal fibroblasts 4-8h post-treatment on C4D15, at Progression of Disease, and at End of Treatment.
The studies will include whole exome sequencing, and the levels/activity of c-Myc, 4EBP1, CK1, and PI3K.

Registration Process

The Study Coordinator will verify eligibility and complete the registration process, by:

- Assigning a patient study number

- Registering the patient on the study
- Confirming registration with the principal investigator

Screening

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):

1) Obtain written informed consent and privacy authorization prior to initiating any protocol-required procedure that is not considered standard of care (See Section 4.3)

2) Review eligibility criteria

3) Review medical chart for past medical/surgical history

4) Record medications and prior antineoplastic treatment regimens

5) Record response to prior treatment regimens

6) Document histopathology from:
   (i) Tumor tissue biopsy at the time of diagnosis
   (ii) Tissue biopsy of relapsed or refractory FL if applicable

7) Document measurable disease sites by the following procedures:
   - CT of the neck, chest, abdomen, and pelvis (PET/CT is optional but preferred)
   - Other imaging studies and/or exams documenting measurable disease sites other than neck, chest, abdomen, and pelvis, if applicable

8) Perform a comprehensive physical examination

9) Assess and record ECOG Performance Status

10) Local laboratory: Collect blood for complete blood count with differential; blood chemistry, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium; liver function tests, including total proteins, albumin, AST, ALT, total bilirubin, direct bilirubin, alkaline phosphate; coagulation tests (PT,PTT,INR); serum β-human chorionic gonadotropin (β-hCG) pregnancy test for women of childbearing potential within 7 days of cycle 1, day 1; serum pregnancy test within 24 hours prior to first dose of the study drug.

11) Calculate creatinine clearance using the glomerular filtration rate (GFR) according to the Cockroft-Gault equation, only if screening serum creatinine is > 1.5 mg/dL: GFR* = (140 – age [years]) x actual body weight (kg)72 x serum creatinine *For female patients, multiply by 0.85

12) Obtain a 12-lead electrocardiogram (ECG) to evaluate for abnormalities.

5. TREATMENT PLAN

Regimen Description

Treatment will be self-administered on an outpatient basis. Patients will take TGR-1202 800 mg, one tablet daily on a continuous basis. Each cycle lasts 28 days. Reported adverse events and potential risks for TGR-1202 are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than the study drug may be administered with the intent to treat the patient's malignancy.

Evaluation and requirements Prior to Each Treatment Cycle

Before the start of each treatment cycle, patients should be reassessed and the following criteria must be fulfilled:

- Absolute neutrophil count (ANC) $\geq$ 1,000/dL
- Platelet count $\geq$ 50,000/dL
- Serum creatinine concentration $\leq$ 2.0 × ULN or $\leq$ baseline, or creatinine clearance > 50 ml/min
- AST (SGOT) and ALT (SGPT) $\leq$ 3.0 × ULN
- Bilirubin concentration $\leq$ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a Bilirubin >1.5 × ULN if no other cause of hyperbilirubinemia is present in the judgment of the treating physician; aPTT and PT not to exceed 1.2 × ULN
- Recovery of any drug-related non-hematological toxicity to Grade 2 or less, unless otherwise indicated

Guidelines for Administration of TGR-1202

- *Method of Administration:* TGR-1202 will be administered orally once daily with food

  Potential Drug Interactions: No Drug Interactions have been reported to date.
- *Pre-medications:* Patients are required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy within 7 days prior to randomization.
- *Anti-viral Prophylaxis*: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent is recommended
- *PCP Prophylaxis:* Bactrim DS 1 tablet 3x per week or Dapsone 100 mg daily or equivalent is recommended.

Final choice of PCP and anti-viral prophylaxis therapy is per investigator discretion

TGR-1202 will be dispensed at the sites by the research coordinator or designee under the direction of the PI or by a pharmacist at the site. Patients must be provided drug in its original container. Patients should be instructed to return any unused tablets when they return the bottle to the site. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle and as needed. Missed doses will be documented in the patients' medical record.

TGR-1202 will be self-administered (by the patient). Tablets should be taken at approximately the same time each day with food. Patients should be instructed to swallow the tablets as a whole and should not chew or crush them.

If a dose of TGR-1202 is missed within 12 hours of its scheduled administration, the patient should take the dose. If it is missed more than 12 hours after the scheduled administration time, the patient should omit that dose and record in the diary. If vomiting occurs, no attempt should be made to replace the vomited dose.

Dispensing of TGR-1202

Before dispensing, the site pharmacist or his/her representative must check that the TGR-1202 is in accordance with the product specifications and the validity is within the re-test date.

The exact dose and the date of administration of TGR-1202 must be recorded within the case report form (CRF), patient's medical records. For the purpose of drug accountability and dosing, a drug diary will be utilized. Any error in drug administration should be recorded (e.g., missed dose) in the CRF.

The Pharmacist or his/her representative should record the date dispensed and patient's number and initials, as well as complete the accountability record in the electronic drug accountability system with information concerning the dispensation of TGR-1202.

Supportive care

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including, but not limited to the use of anti-emetics, anti-diarrheal, antipyretics, anti-histaminics, analgesics, antibiotics, growth factors, blood products, and other drugs not prohibited during the study period.

- Use of myeloid growth factors and erythropoiesis-stimulating agents:
  Colony stimulating factors (i.e., filgrastim, peg-filgrastim, and sargramostim) may be used according to the 2006 American Society of Clinical Oncology (ASCO) guidelines.(Smith et al., 2006) Peg-filgrastim should only be used if the time to the next dose is ≥14 days. Anemia may be managed with erythropoiesis stimulating agents according to the ASCO/ASH guidelines.(Rizzo et al., 2010) Patients with pre-existing chronic anemia treated with epoetin or darbepoietin, may continue to receive such agents during the study period, but should not start them once on study.

- Specific supportive care issues:

  Diarrhea: Diarrhea should be treated promptly with appropriate hydration and antidiarrheal agents such as 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. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each non-formed stool. The daily dose of loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. If the treating physician diagnoses the diarrhea as grade 3 or 4 by CTCAE v4.0, TGR-1202 should be held. If colitis is suspected colonoscopy should be considered if it can be done safely.

  - **Nausea/emesis:** Nausea and emesis should be treated with standard anti-emetics, including 5-hydroxytryptamine 3 serotonin receptor (5-HT3) antagonists, prochlorperazine, metoclopramide, or benzodiazepines. Patients should be encouraged to maintain adequate oral fluid intake during therapy. Dexamethasone should not be administered as an antiemetic.

  - **Anemia:** Treatment with TGR-1202 can cause anemia. Transfusions or erythropoiesis stimulating agents may be utilized as clinically indicated for the treatment of anemia and should be clearly noted as concurrent medications. Dose modifications for anemia are outlined in section 6.3.

  - **Thrombocytopenia:** Treatment with TGR-1202 can cause thrombocytopenia. Transfusion of platelets may be used if clinically indicated. TGR-1202 dose modification guidelines for thrombocytopenia are outlined in section 6.

  - **Neutropenia:** Neutropenia can occur during treatment with TGR-1202. Blood counts should be monitored regularly as outlined in the protocol and additional testing should be obtained when indicated, according to standard cli**n**ical practice. Colonystimulating factors, including G-CSF, pegylated G-CSF or GM-CSF may be utilized as clinically indicated. TGR-1202 dose modifications for neutropenia are outlined in section 6.

  - **Infections:** Serious infections, including pneumonia and febrile neutropenia have been reported during treatment with TGR-1202. Any suspected infection should be promptly managed. Hospitalization should be considered when clinically appropriate.

  - **Mucositis:** stomatitis has been reported during TGR-1202 therapy. Lidocainecontaining oral solutions may be used as needed to ameliorate the symptoms thereof.

- **Tumor lysis syndrome prophylaxis**: Subjects should receive allopurinol and other treatment considered appropriate for tumor lysis prophylaxis during cycle 1 as deemed necessary by the treating physician.

Concomitant Medication Guidelines

All medications taken within 30 days of screening and medications and supportive therapies that are administered during the study must be recorded in the patient's CRF and in the source documents. Concomitant medications for other medical conditions are permitted as clinically indicated. Over-the-counter and herbal products should not be taken during the study period without prior consultation with the PI.

The following concomitant medications are prohibited during the study period:

- Any antineoplastic agent other than TGR-1202
- Prednisone at a stable dose of >10 mg daily
- Radiation therapy; palliative radiation therapy to a pre-existing symptomatic lesion may be allowed on a case-by-case basis after discussion with the study PI

Duration of Therapy

Treatment may continue until one of the following criteria applies:

- Disease progression
- Unacceptable AE(s) □ Withdrawal of consent
- Changes in the patient's condition that render continuation of the study drug unacceptable in the judgment of the treating physician
- An event that in the judgment of the treating physician warrants discontinuation of therapy
- Study drug will be made available to responding patients for a total of three years from initiation of therapy. If TGR-1202 becomes commercially available during the active period on study, an attempt will be made to obtain this agent through commercial insurance. If coverage is not available, it will be provided for a period of three years as stated above.

Duration of Follow Up

Patients will have an end-of-study visit 4 weeks ±1 week after the last dose of the study drug to evaluate safety. Patients will be further followed every three months for one year, or until they begin a new treatment for their disease, for evaluation of delayed toxicity. Patients removed from study for unacceptable AE will be followed until resolution or stabilization of the AE. Further follow-up should be performed according to standard clinical practice.

For patients who achieve stable disease or better after 6 cycles of therapy, tumor assessment will be performed by medical history, physical exam, complete blood count with differential and blood chemistries every 3 months, and CT (PET/CT optional but encouraged) at least every 6 months, until progression of disease occurs.

Criteria for Removal from Study

Patients will be removed from treatment when any of the criteria listed in Section 5.3 applies. The reason for and date of patient removal must be documented in the CRF.

Subjects/patients may withdraw consent 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 due to administrative and/or safety reasons. The investigator or study coordinator will notify the appropriate parties within 2 business days of becoming aware of an adverse event causing withdrawal of the subject from the study (Section 7). 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

- For a new treatment cycle to begin, patients must meet the criteria outlined in section 5. Moreover, all other toxicity must have returned to grade ≤2. If either of these conditions are not met, the study drug will be held.

- If interruption of study drug lasts for more than 28 days, treatment should be discontinued and the subject should be removed from the study (please contact the study chair to discuss longer interruptions).

- Patients who experience toxicity and require the study drug to be withheld may not be candidates for biopsy. Patients who miss 4 or more doses of drug prior to a planned biopsy should be considered ineligible for biopsy. The treating physician will make the ultimate decision in this regard.

Dose Modifications

Patients will be monitored continuously for toxicity while on study therapy. Toxicity will be assessed using the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) grading scale. If a patient has an adverse event of particular severity or had an adverse event at least possibly related to study drug, then dose modifications will be made according to the guidelines.
Deviations from these guidelines may occur only if agreed upon by the Principal Investigator. There should be no attempt to make up for doses omitted due to toxicity.

A maximum four (4) week delay of treatment for recovery from toxicity is allowed to recover from hematologic toxicities to ≤ Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If greater than a four (4) week delay is necessary, then the patient should discontinue treatment

and continue to be followed for progression. If a patient withdraws consent or has documented progression, an end of study visit should be completed.

Recommended treatment interruptions/holds or dose modifications are summarized below and may be based on the clinical judgment of the Investigator with notification to the Principal Investigator. For an individual patient, dose reductions and discontinuations may be more conservative than indicated. (i.e., to dose-reduce or discontinue for non-hematologic toxicity of lower grades) based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor.

Summary of Dose Holds for Treatment-Related Toxicities

NCI-CTCAE Grade	**Dose Delay and/or Modification**
Hematologic Adverse Event	
Neutropenia	
Grade ≤2 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 3 neutropenia	Maintain current dose, consider supportive care. If recurrence or persistent Grade 3, the next lower dose level will be allowed.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay TGR-1202 until Grade ≤3 and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider supportive care. If delay is > 4 weeks discontinue study drug. If recurrence after rechallenge, resume at the next lower dose level at discretion of the investigator.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose level and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay TGR-1202 until Grade ≤3; thereafter, resume at full dose. Consider supportive care intervention as warranted. If delay is > 4 weeks, discontinue TGR-1202. If recurrence after rechallenge, resume at the next lower dose level.
Pulmonary & Related Infections*	
Grade ≥2	Withhold TGR-1202 as warranted, provide supportive care. Resume at full dose. If recurrence after rechallenge, resume at the next lower dose level.
*While pneumonitis has been minimal with TGR-1202, it is a reported adverse event associated with other PI3K delta inhibitors. PCP and anti-viral prophylaxis is required for any study patient.	
All Other Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level

Grade ≥3	Withhold TGR-1202 until Grade ≤2. Resume at full dose. If recurrence after rechallenge, resume at the next lower dose level.

Study Drug Dose Levels

Study Drug	Starting Dose	1st Dose Reduction	2nd Dose Reduction
TGR-1202	800 mg	600 mg	400 mg

If a patient requires a dose reduction of TGR-1202 due to study drug related toxicity, the dose may not be re-escalated. If further evaluation of the toxicity reveals the event was not related to TGR-1202, this must be recorded in the medical record and dose re-escalation to the next higher dose level may be considered at the discretion of the investigator.

Ordering TGR-1202

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

Upon receipt of drug supplies, the Pharmacist or the designee from the site should update the accountability forms for TGR-1202. If any abnormality on the supplied bottles (TGR-1202) is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Safety Evaluation Procedures

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product; such occurrence does not necessarily have a causal relationship with this treatment. An adverse event is, therefore, any unfavorable and unintended change in the structure, function, or chemistry of the body that is 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, is also an adverse event.

Adverse events may occur at any point during the study period, including pre-treatment, treatment and follow-up period as specified by the protocol.

Adverse events will be graded and recorded throughout the study period according to NCICTCAE, version 4.0. Toxicities will be characterized in terms of duration, intensity, and time to onset. Safety endpoints will include all types of adverse events, in addition to laboratory safety assessments, ECOG performance 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 study drug, patient care, and outcome.

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

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

The STUDY CALENDAR (Section 10) provides specific details on collection time points.

Serious Adverse Events (SAE)
SAE as defined in the following FDA website will be reported to the FDA:
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm

Details are listed in the Appendix 8.

Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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.

Very Common (≥ 10%) Blood and lymphatic system disorders: Neutropenia
Gastrointestinal disorders: Nausea, Diarrhea, Vomiting
General disorders and administration site conditions: Fatigue **Metabolism and nutrition disorders:** Decreased appetite **Skin and subcutaneous tissue disorders:** Rash

Common (≥ 1% and < 10%)

Blood and lymphatic system disorders: Anemia, Febrile neutropenia, Leukocytosis, Thrombocytopenia

Ear and labyrinth disorders: Tinnitus
Eye disorders: Vision Blurred, Visual Acuity Reduced
Gastrointestinal disorders: Abdominal distension, Abdominal pain, Constipation, Dry mouth, Dyspepsia, Eructation, Hypoaesthesia oral, Mouth Ulceration, Flatulence, Gastroesophageal reflux disease, Paraesthesia oral, Colitis
General disorders and administration site conditions: Asthenia, Chills, Malaise, Oedema peripheral, Pyrexia, Mucosal inflammation **Hepatobiliary disorders:** Hyperbilirubinaemia
Infections and infestations: Candida infection, Lung infection, Oral candidiasis, Pneumonia, Upper respiratory tract infection, Sinusitis
Investigations: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Blood lactate dehydrogenase increase, Blood phosphorus increased, Blood sodium increased, Blood uric acid increased, International normalized ratio increased, Lymphocyte count increased, Weight decreased
Metabolism and nutrition disorders: Dehydration, Hyperglycaemia, Hyperlipidaemia, Hypertriglyceridaemia, Hypokalaemia, Hyponatraemia, Hypophosphataemia, Hypomagnesaemia
Musculoskeletal and connection tissue disorders: Arthralgia, Muscle spasms, Muscular weakness, Myalgia, Pain in extremity, Pain in jaw
Nervous system disorders: Dizziness, Dysgeusia, Headache, Memory impairment, Neuropathy peripheral, Somnolence, Tremor, Peripheral sensory neuropathy
Psychiatric disorders: Anxiety, Insomnia, Libido decreased, Delirium, Parasomnia
Reproductive system and breast disorders: Erectile dysfunction
Respiratory, thoracic and mediastinal disorders: Cough, Dyspnea, Epistaxis, Hypoxia, Respiratory failure, Sinus congestion
Skin and subcutaneous tissue disorders: Alopecia, Dermatitis acneiform, Night sweats, Pruritus
Vascular disorders: Hot flush

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
Infections and Infestations: Infection

Safety analyses

Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the safety population. Safety variables will be tabulated and presented by the dose of TGR-1202 study drug actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

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 classified as 'Unexpected' or 'Expected' 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.

Expedited Adverse Event Reporting

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

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to the Sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from Cycle 1/Day 1 through the 30-day follow-up period after the last study treatment. Sponsor or designee should be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, see the appropriate form.

All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to the sponsor as SAEs within the CRF and followed until resolution (with autopsy report if applicable).

Progression or death due to disease progression should be reported by the investigator as a SAE only if it is assessed that the study drugs caused or contributed to the disease progression (i.e. by a means other than lack of effect). Unrelated events of disease progression should be captured on the appropriate CRF.

The investigator must review and sign off on the SAE data on the SAE report. The SAE should be reported to the Sponsor (or Sponsor designee). When an SAE is reported to the sponsor or designee, the same information should be entered on the CRF within 24 hours (1 business day). Transmission of the SAE report should be confirmed by the site personnel submitting the report. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the sponsor or designee as soon as it is available; these reports should be submitted using the appropriate SAE form.

Investigators should report SAEs and follow-up information to their responsible Institutional Review Board (IRBs)/Independent Ethics Committee according to the policies of the responsible IRB (Research Ethics Committee).

Sponsor SAE Reporting Requirements

Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

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

Report of Adverse Events to the Institutional Review Board (IRB)

Reportable information should always be reported by the PI directly to the IRB within 5 working days since the PI's first knowledge of the event or new information.

Investigator Reporting to the FDA

The investigator is responsible for reporting any SAEs to the FDA. SAEs that are **unlisted/unexpected, at least possibly related 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 since first

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 since first 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

TG therapeutics shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of the 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 promptly notify his/her IRB/ethics committee 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 TG and the IRB/EC, on file.

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.

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:

Table 2: 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	Thrombocyotopenia <7 days without bleeding	4	No	Yes

Pregnancy on Study

During the course of the study, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix 4) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

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

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must notify the Study Chair or Medical Monitor as soon as possible.

If a patient becomes pregnant while enrolled in the study, an SAE form should be completed and submitted to the Sponsor. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor.
Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting.

Study Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment (TGR-1202) that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the corresponding SAE form, and following the same process described for SAEs. If a study drug overdose occurs, patients should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

Secondary Malignancy

Any secondary malignancy event must be reported via the SAE form (in addition to the routine AE reporting mechanisms). Any malignancy possibly related to cancer treatment should also be reported via the routine reporting mechanisms outlined in the protocol.

Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. New onset adverse events occurring up to 30 days after study completion or patient withdrawal will be captured. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the CRF. Follow up of these events will be performed according to the same procedures as described above for AEs observed during the study period.

After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.2.

TGR-1202

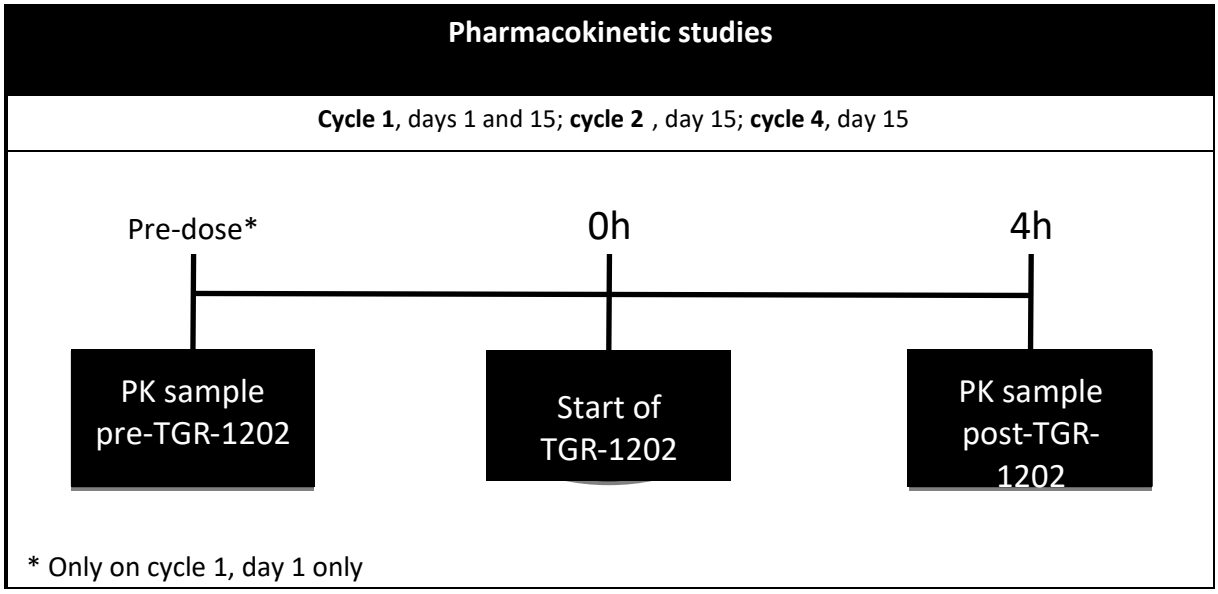
Classification:	Phosphatidylinositol-3-Kinase (PI3K) Delta Inhibitor
Formulation:	See Investigator Brochure
Mode of Action:	Irreversibly inhibits activity of the Class I Delta isoform of PI3K
How Supplied:	TGR-1202: 200 mg tablets
Storage:	Store at 25°C. Excursions permitted 15°C to 30°C.
Stability:	Retest dates will be provided periodically by Sponsor.
Route of Administration:	Oral
Packaging:	TGR-1202 is provided in HDPE bottles each containing 30 tablets and a silica gel canister as a desiccant.
Availability:	TGR-1202 is available from TG Therapeutics.

9. PHARMACOKYNETIC/PHARMACODYNAMIC STUDIES

Pharmacokinetic (PK) Studies

Up to 5 ml of blood will be collected in Lithium Heparin tubes for isolation of plasma at PreTreatment on C1D1, and 4h post-treatment on C1D1, C1D15, C2D15 and C4D15 (Figure 2).

Figure 2. PK schedule



Blood samples will be stored on ice until centrifuged. After centrifuge, plasma will be stored in polypropylene screw top tube at -70ºC until evaluation by liquid chromatography.

Pharmacodynamics Studies

Collection of specimens

Participation in correlative studies is mandatory for all patients. In addition to the mandatory correlative studies for all patients, there will also be optional correlative studies, which will be performed under a separate section of the informed consent form.

Missing 4 doses or more 1 week prior to the planned biopsy on Cycle 2 Day 15 could render that patient ineligible for biopsy, but that decision will be made at the discretion of the treating physisican and Study PI.

Mandatory correlative studies include the following:

For PK studies:

1. Collection of blood at Pre-treatment (approx. 3 ml).

2. Collection of blood at 4h post-treatment on C1D1, C1D15, C2D15, and C4D15 (total approx. 12 ml).

For PD studies:

1. Collection of blood at Pre-Treatment.
   Collection of blood at 4h post-treatment on C1D1, C1D15, C2D15 and C4D15. The studies will include T cell panel such as T-reg, expression of CD47 and PD-L1, cytokines such as IL-10 and IL-12, and PI3K targeting.
2. Collection of tumor tissues, blood cells, and buccal fibroblasts pre-treatment and 4-8h posttreatment on C2D15.
   The studies will include whole exome sequencing, and the levels/activity of c-Myc, 4E-BP1, CK1, and PI3K.

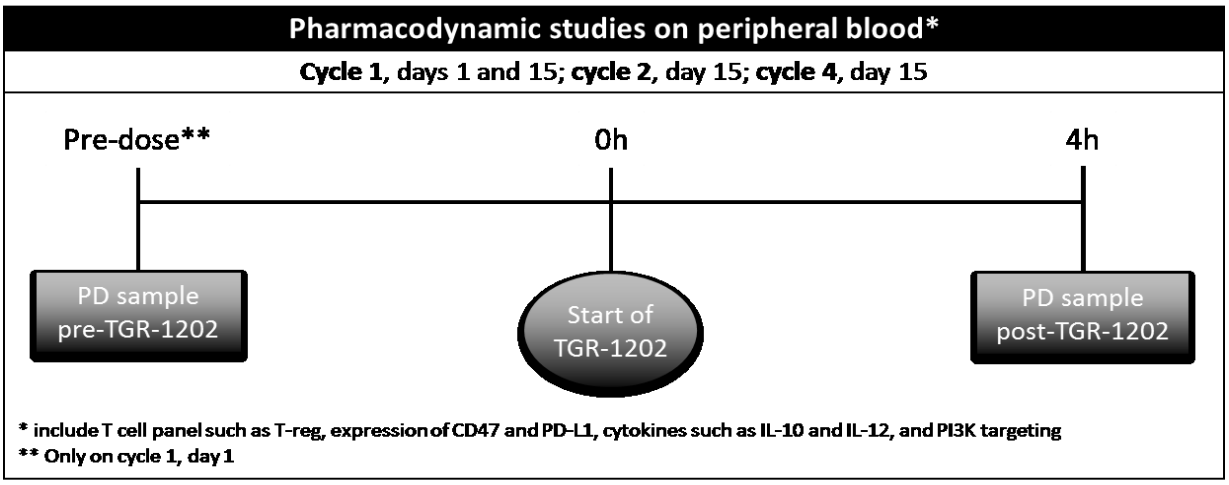
Missing 4 doses or more 1 week prior to the planned biopsy on C2D15 could render that patient ineligible for biopsy, but that decision will be made at the discretion of the treating physician and Study PI.

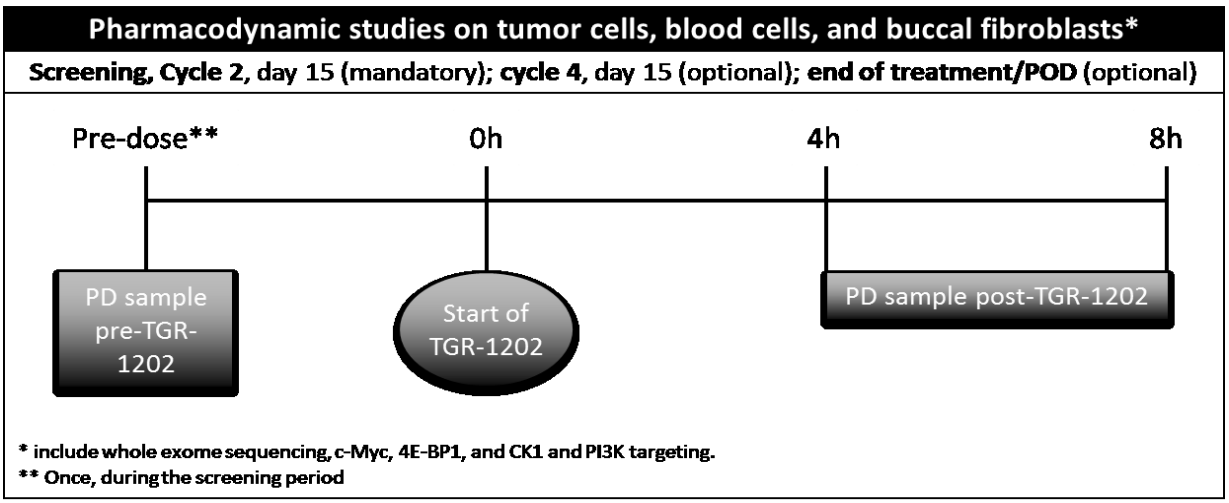
Optional correlative studies are listed below:

Collection of tumor tissues and buccal fibroblasts 4-8h post-treatment on C4D15, at Progression of Disease, and at End of Treatment.

The studies will include whole exome sequencing, and the levels/activity of c-Myc, 4E-BP1, CK1, and PI3K.

Figure 3. PD schedule





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 optional studies as explained above.

Fine Needle Aspirations (FNA): A series of FNAs will be performed on palpable tumors in consenting patients as a function of drug exposure.

Tumor Tissue Biopsies: The biopsies will be performed by a surgeon or an interventional radiologist, as appropriate. If multiple lymph nodes are available, the safest lymph node will be selected. A cytopathologist will evaluate the biopsy for tumor cells microscopically at the time of the biopsy. Correlative studies will be performed on de-identified tissue samples. Tissue will be labeled only with the protocol-specific unique identifier.

Bone Marrow Biopsy: a bone marrow aspirate and biopsy will be performed pre-treatment if necessary to determine the stage of the disease.

Handling of Specimens
Specimens required for clinical diagnosis will be submitted to Pathology per standard patient care practice.

Research specimens will be handled as explained below:

- Blood will be processed to isolate the serum and mononuclear cells. The specimens may then be used immediately for correlative studies such as flow cytometry or stored for future studies in bulk with all patient samples. Stored samples will be either frozen at -80 degrees or refrigerated at 4 degrees Celsius.

- Bone marrow and other tissue aspirate samples will be processed to isolate the mononuclear cells enriched for viable lymphoma cells. The specimens may then be used for correlative studies such as flow cytometry immediately or stored for future studies in bulk with all patient samples.

- Samples from core biopsy (e.g. bone marrow, skin, lymph nodes or other lymphoid tissue) may be snap frozen in a dry ice/alcohol bath or liquid nitrogen, or processed for the isolation of viable lymphoma cells.

- Fibroblasts will be isolated from buccal swabs, and frozen or refrigerated as above.

- Cellular samples will be used immediately or snap frozen, depending on the type of correlative studies. For example, ex vivo pharmacological studies require fresh isolated lymphoma. mRNA and DNA may be extracted from frozen or fixed cellular or tissue specimens.

Biomarker studies

A major goal of this study is to determine the genetic, and biochemical heterogeneity in the follicular lymphoma cells, and discover the effects of distinct cellular and molecular alterations on patient response to TGR-1202. To this end, we will perform the following studies using patient samples:

- Conduct DNA and RNA sequencing and gene expression studies on samples before and after treatment with TGR-1202.

- Compare and contrast the effects of TGR-1202 on mRNA translation in normal fibroblasts and lymphocytes versus lymphoma cells from the same patient, using the state of the art technology of ribosome profiling.

- Compare and contrast the effects of TGR-1202 on the mTOR signaling in normal fibroblasts and lymphocytes versus lymphoma cells from the same patient, using Western blot and IHC staining.

- Develop an *in vitro* system to test responsiveness to TGR-1202 in primary lymphoma cells isolated fresh from patients.

- Test synergy of TGR-1202 with drugs targeting pathways that interact with PI3K, using lymphoma cell lines and primary FL cells from patients on study

- Determine the effects of TGR-1202 on cytokine production in the blood of patients treated on study

- Develop an *in vivo* model of FL by directly implanting FL cells from patient biopsies into mice patient derived xenograft (PDX) model.

10. STUDY CALENDAR

Baseline evaluations are to be conducted as indicated in the table below, prior to start of protocol 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.

(All study assessments allow a +/- 3 day window)

Cycle		1				2+				
	Screening	D1	D8	D15	D22[n]	D1	D15	End of treatment[k]	End of Study (4 weeks after last dose)	Follow - up[m]
Eligibility, safety monitoring, efficacy										
Informed Consent	X[a]									
Demographics	X[a]									
Medical History	X[a]									

EKG	X[a]									
Concurrent Medications	X[b]	X[e]	X	X	X	X		X	X	
Physical exam	X[b]	X[e]	X	X	X	X		X	X	X
Vital Signs, weight	X[b]	X	X	X	X	X		X	X	X
Performance Status	X[b]	X	X	X	X	X		X	X	X
CBC w/ differential	X[b]	X[e]	X	X	X	X		X	X	X
Chemistries[c,g]	X[b]	X[e]	X	X	X	X		X	X	X
Coagulation tests	X[b]									
Creatinine clearance	X[b]									
Serum □-hCG[d]	X[b]	X								
CT (or PET/CT)	X[a]					X[f]				X[f]
Bone Marrow Biopsy	X[a]					X[o]		X[p]		
Drug Administration										
TGR-1202 800 mg		X	→	→	→	→	→			
Toxicity Assessment		X	X	X	X	X		X	X	
Correlative Studies										
Blood for PK		X[i]		X[i]			X[i]			
Blood for PD		X[h]		X[h]			X[h]			
Buccal swab	X[l]						X[l,p]	X[p]		
Lymph Node/Bone Marrow Biopsy	X[a]						X[l,p]	X[p]		

a. To be done within 4 weeks of treatment start date.
b. To be done within 1 week of treatment start date. Nurse practitioner can perform exams after cycle 1.
c. Chemistries include: Chem *, Mg, K, Hepatic Function Panel, and LDH.
d. To be done within 1 week of treatment start date for patients of childbearing age.
e. Not necessary if conducted within 72 hours of screening assessment.
f. CT scan of the neck, chest, abdomen, and pelvis (and/or PET/CT) at the end of Cycle 2 and 6. Thereafter, restaging CT scans will be repeated every 4 months, or every 6 months if a complete response is achieved. To be performed on every cycle.
g. Sodium, potassium, chloride, calcium, and glucose are part of the electrolyte assessment at every time point.
h. Pre-treatment on C1D1, and 4 hours post-treatment on C1D1, C1D15, C2D15 and C4D15
i. Pre-treatment on C1D1, and 4 hours post-treatment on C1D1, C1D15, C2D15 andC4D15
j. To be done within 4 weeks of treatment stop date.
k. To be performed pre-treatment and 4-8 hours post-treatment on C2D15 (mandatory), and C4D15, end of treatment and progression of disease, if applicable (optional).
l. May be done +/- 7 days.
m. May be done +/- 3 days.
n. To be performed after cycle 2 to confirm response if positive at baseline.

o. If positive at baseline and hasn't been performed to confirm CR
p. Optional collection of buccal fibroblasts, bone marrow, and Lymph Node Biopsy will be allowed post-treatment on C4D15, at Progression of Disease, and at End of Treatment.

(All study assessments allow a +/- 3 day window)

11. MEASUREMENT OF EFFECT

The primary objective of this study is to evaluate the ORR of the study drug. Patients with measurable disease will be assessed by standard criteria. Patients will be re-evaluated at the end of cycle 2 and cycle 6, thereafter every 4 months, or every 6 months if a CR is achieved. Response will be evaluated with physical exam, computerized tomography (CT) and tissue biopsies as defined in the 2014 Lugano classification.(Cheson et al., 2014b) PET/CT is optional, but strongly encouraged.

Evaluation of response:

Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity starting from Day 1 of Cycle 1.

Evaluable for objective response: Patients who have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below (Table 3). Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in two dimensions (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 (for sites of measurable disease, see Appendix 7).

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

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, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all nonmeasurable.

Target lesions. All measurable lesions, up to a maximum of 6, that are representative of all involved organs, should be identified as target lesions and measured and recorded at baseline. If PET/CT is performed, target lesions should be selected on the basis of their FDG avidity (High SUV lesions will be prioritized, even if not the largest lesions), 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.

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 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. As a general rule 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 medical photography that includes a ruler to measure 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. Imaging of head and neck tumors and those of the extremities will be performed according to institutional specific protocols.

Ultrasound (US) Will not be used for disease assessment

Response Criteria

Response assessment in NHL

Responses will be evaluated using clinical parameters, CT scan (PET scan is optional) and bone marrow biopsy according to the 2014 Lugano Classification (Cheson et al., 2014a) as outlined in Table 3.

Table 3. Revised Criteria for Response Assessment (Cheson et al., JCO 2014)

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† 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	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No extralymphatic sites of disease

	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	
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
Non-measured lesion	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value
Organ enlargement	At end of treatment, these findings indicate residual disease	When no longer visible, 0 x 0 mm. For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
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
Non-measured lesion	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
Non-measured lesion	None	New or clear progression of preexisting non measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If	- Regrowth of previously resolved lesions - A new node >1.5 cm in any axis
	uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	- 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 under treatment). 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.

Overall Response Rate

Overall Response Rate (ORR) will be defined as the sum of CR rate and PR rate based on evaluation of best response in each patient.

Evaluation of Best Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The best overall response will be used as the reference to define progression of disease, should this occur.

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).

Data Reporting

Monitoring

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

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.

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.

Investigator Reporting Responsibilities

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

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 TG Therapeutics or its 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.

Protocol amendments

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

Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that specific 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 thoroughly and 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 and when possible deviation will not be implemented until IRB approval is obtained..

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

13. STATISTICAL CONSIDERATIONS

Study Design/ Primary Endpoints

This is a phase 2 study of oral TGR-1202 in patients with relapsed or refractory follicular lymphoma. (See figure 1 for study plan flow chart)

Sample Size/Accrual Rate

The phase II will allow for a total accrual of 20 patients.

We estimate accrual of an average of 1-3 patients per month, with a goal of completing accrual within 12 months.

Based on the phase I study of TGR-1202, the ORR for TGR-1202 will be 60%. The ORR is 33% based on historical control drugs, such as lenalidomide. We estimate that 20 patients will be needed to have a power of 87% to reject the null hypothesis that ORR=0.33 in favour of alternative hypothesis ORR=0.6 with one side type I error rate of 0.10.

Analysis of Primary and Secondary Endpoints

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) will be used. Overall response rates will be measured upon completion of the study with exact 95% confidence intervals.

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APPENDICES:

Appendix 1. Ann Arbor Classification

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E

NOTES:
1. For each stage, A= no symptoms; B= Fever (>38C), drenching sweats, 10% body weight loss over 6 months 2. For Stages I to III: E = Involvement of a single, extranodal site contiguous or proximal to known noda site
Adapted from: Armitage JO. CA Cancer J Clin.2005;55:368-376.

Appendix 2. Revised Staging System for Primary Nodal Lymphoma

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

* A variety of sizes have been suggested for the definition of bulky disease in NHL. However, none of the proposed sizes have been validated in the current therapeutic era. Therefore, it is recommended to record the longest measurement by CT scan. Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
Adapted from: Cheson BD, Fisher RI, Barrington SF, et al. J Clin Oncol. 2014;32:3059-3067

Appendix 3. Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

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

Ref: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6): 649-55

Appendix 4. Contraceptive Guidelines and Pregnancy

Women Not of Childbearing Potential are Defined as Follows:

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

Contraceptive Guidelines for Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 30 days after stopping treatment. The highly effective contraception is defined as either:

- True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the

reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomised male partner should be the sole partner for that patient.
- Oral contraception, injected or implanted hormonal methods.
- Use of a combination of any two of the following (a+b):
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
  - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

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

1. Female condom
2. Natural family planning (rhythm method) or breastfeeding
3. Fertility awareness
4. Withdrawal
5. Cervical shield

Women of child-bearing potential must have a negative serum pregnancy test within 5 days of initiating treatment.

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, for five half-lives (8 days) after stopping treatment and for additional 12 weeks (3 months in total after study drug discontinuation) and should not father a child in this period.

Pregnancies

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

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

Appendix 5. Interpretation of Hepatitis B serologic test results

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

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

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

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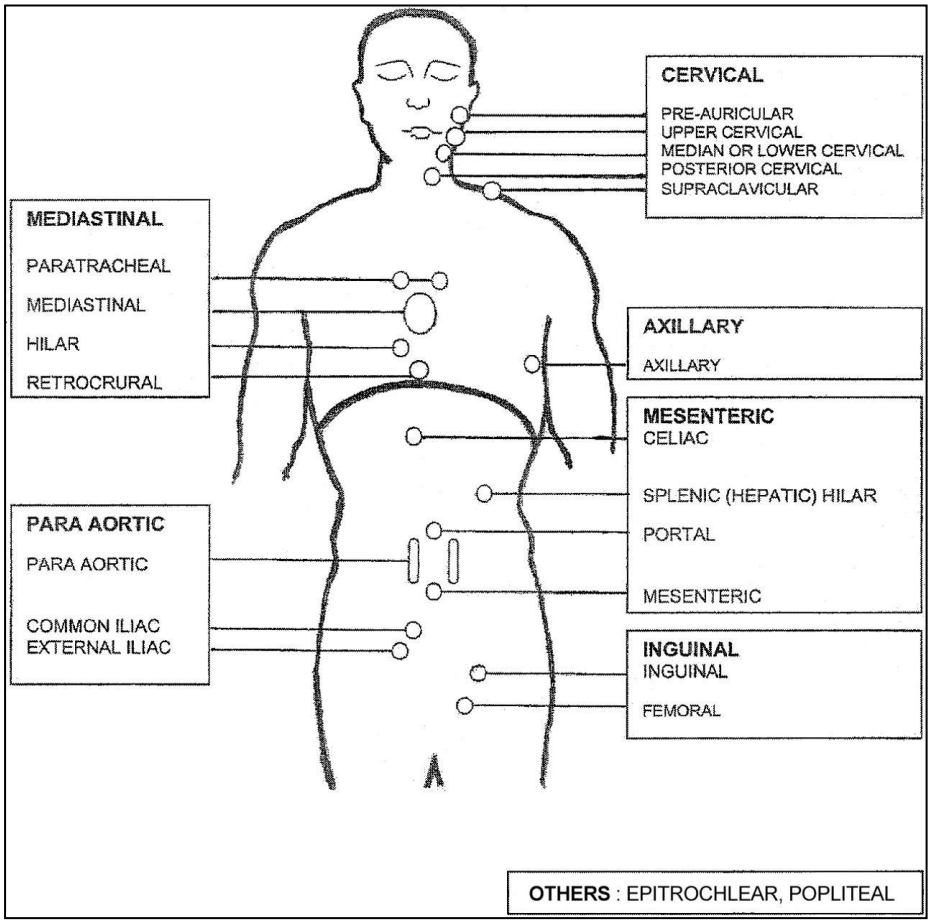
- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part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

Appendix 6. New York Heart Association Functional Classification

Class	Functional capacity: how a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain
II	Patients with cardiac disease resulting in slight limitation physical activity. They're comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patient with cardiac disease resulting in marked limitation of physical activity. They're comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain
IV	Patients with cardiac disease resulting and inability to carry on any physical activity without discomfort. Intense of heart failure or the angina syndrome maybe present even at rest. If any physical activity undertaken, discomfort increases.

Appendix 7. Measurable Lymph Node Locations

Ref: Solal-Celigny P, et al. Blood. 2004;104:1258-1265



Appendix 8. Groupe d'Etude des Lymphomas Folliculaires (GELF) Criteria

Presence of one or more of the following:
Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm
B symptoms*
Splenomegaly (enlarged spleen)
Pleural effusions or peritoneal ascites
Cytopenias (leukocytes < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L)
Leukemia (> 5.0 x 109/L circulating malignant cells)

* include unexplained and persistent: Fever and chills, drenching night sweats, fatigue, pruritus/skin itchiness, weight loss

NOTE: These criteria provide general guidance. The need for treatment can vary in individual patients
Adapted from: Brice P, Bastion Y, Lepage E, et al. J Clin Oncol 1997;15(3):1110-7

Appendix 9. Follicular Lymphoma International Prognostic Index (FLIPI)

Factor	Criterion
Age	≥ 60 years
Ann Arbor stage	III-IV
Hemoglobin level	<12 g/dL
Serum LDH level	>upper limit of normal
Number of nodal sites	≥5

Number of factors	Risk
0-1	Low
2	Intermediate
≥3	High

Adapted from: Solal-Celigny P, et al. Blood. 2004;104:1258-1265

Appendix 10: SAE

The FDA website classify the following as SAE:
An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA when the patient outcome is:

Death

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.