Official Title:	A Phase II Trial of Umbralisib and Pembrolizumab in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma
NCT Number:	NCT03776864
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	10/29/2021

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
FRED HUTCHINSON CANCER RESEARCH CENTER
SEATTLE CANCER CARE ALLIANCE

A Phase II Trial of Umbralisib and Pembrolizumab in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

Protocol Version 4.0 Dated 12 November 2020

Sponsor/Principal Investigator:
Ryan Lynch, MD
Assistant Professor, University of Washington
Assistant Member, Fred Hutchinson Cancer Research Center
Seattle Cancer Care Alliance
825 Eastlake Ave. E, CE3-300
Seattle, WA 98109
Telephone: (206) 606-1739

Statistical Consultant
Qian (Vicky) Wu, PhD- Assistant Member, FHCRC

This trial is supported by a grant from TG Therapeutics, Inc.
Tracking Number: TGR-NTG-001

Previous Protocol Version (Dates):
1.0 dated 01 March 2019
2.0 dated 07 October 2019
3.0 dated 20 August 2020

SCHEMA

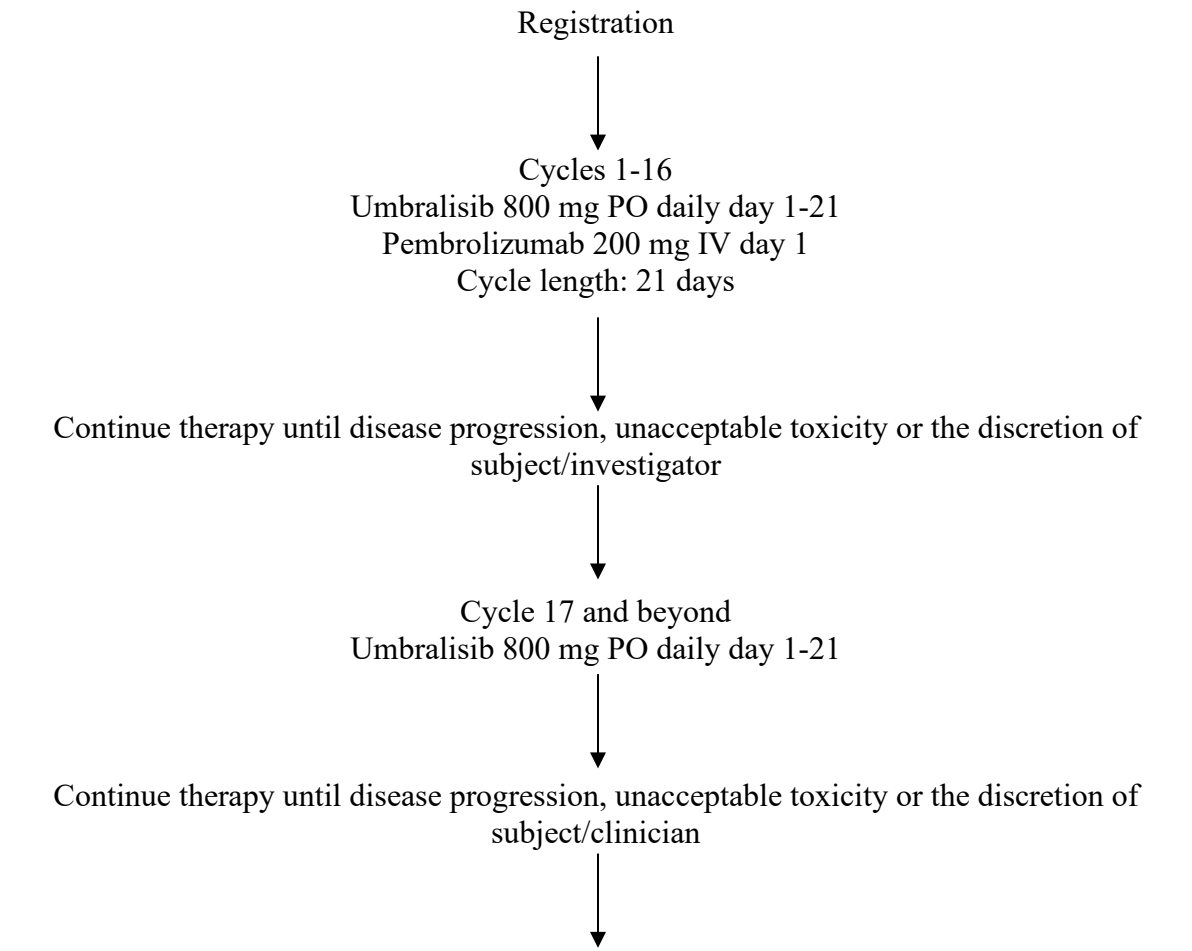
Registration
Cycles 1-16
Umbralisib 800 mg PO daily day 1-21
Pembrolizumab 200 mg IV day 1
Cycle length: 21 days
Continue therapy until disease progression, unacceptable toxicity or the discretion of subject/investigator
Cycle 17 and beyond
Umbralisib 800 mg PO daily day 1-21
Continue therapy until disease progression, unacceptable toxicity or the discretion of subject/clinician
Follow up for 1 year after enrollment for survival and remission status for subjects on study for < 1 year

TABLE OF CONTENTS:

1.0 OBJECTIVES

1.1 Primary objective: To estimate the proportion of subjects with relapsed/ refractory classical Hodgkin Lymphoma (CHL) who achieve a complete response (CR) with a regimen of umbralisib (oral, daily) and pembrolizumab (IV, day 1 of 21-day cycles).

1.2 Secondary objective: Overall response rate (ORR) and safety of this regimen.

1.3 Exploratory objective: 1-year overall survival (OS) and progression free survival (PFS), association of biomarkers with response.

2.0 BACKGROUND

Main Scientific Question:

The fundamental scientific question of this proposal is to evaluate the efficacy and safety profile of dual targeting of the immune microenvironment by means of PD1 blockade and PI3Kδ inhibition as well as direct targeting of the tumor cell by blocking PI3Kδ in patients with relapsed/ refractory classical Hodgkin Lymphoma (CHL). Single agent anti-PD1 therapy can induce high overall response rates in CHL, but few patients achieve complete remissions[1,2]. Likewise, single agent PI3Kδ inhibition can induce responses in about 20% of patients with relapsed/refractory CHL[3]. Preclinical data indicate that inhibiting PI3Kδ inactivates regulatory T-cells (Tregs) and potentially myeloid-derived suppressor cells (MDSCs)[4], which may further contribute to the antitumor effect of PD1-inhibition. This trial will build on this work by testing the safety of dual targeting of the immune microenvironment by means of combining the anti-PD1 agent pembrolizumab (approved for relapsed CHL) and a novel PI3Kδ inhibitor, umbralisib. This question will be addressed by means of a clinical trial to assess the CR rate of this combination in relapsed/refractory CHL. Secondary and exploratory endpoints include safety with attention paid to immune-related toxicities as well as additional efficacy endpoints of this combination in patients who are anti-PD1 naïve and anti-PD1-refractory. Correlative endpoints may include assessment of PD1 and PDL1 by IHC, del 9p24.1 by FISH, and monocytic MDSC (CD11b+CD14+CD33+) and granulocytic MDSC (CD11b+CD66b+) by flow cytometry, cytokine profiles, and circulating tumor DNA.

Rationale and background for scientific question:

Unmet Medical Need:

Relapsed CHL remains an area of unmet medical need despite the approval of three novel agents in the last 7 years (brentuximab vedotin [BV] – 2011, nivolumab- 2016, pembrolizumab- 2017). Only about 1/3 of patients with relapsed CHL will achieve a CR following BV and ~10% will attain long term remissions[3]. Likewise, pembrolizumab and nivolumab induce complete remissions in ~15% of patients and the long-term durability is unknown[1,2]. Despite the clear benefit of these agents, most

patients will not achieve complete remission or be cured, and improved options are needed for relapsed or refractory CHL.

CHL as an immune responsive malignancy:

CHL represents the prototype of tumor immune evasion with often <1% of the involved node representing malignant Reed-Sternberg cells. The majority of the tissue is made of an ineffective inflammatory infiltrate predominantly composed of T-cells. Early data indicated that expression of PDL1 in tumor cells was associated with poor outcome[5], leading to evaluation of PD1 blockade in this setting (as described above). However, methods to safely augment the anti-tumor immune response to improve on the low complete remission rates observed with single agent PD1 blockade have yet to be demonstrated. This proposal will evaluate a novel method of augmenting the immune response via concurrently targeting the PI3Kδ pathway along with PD1 blockade.

PI3K inhibition in CHL:

PI3K is known to mediate key components of cellular signaling. PI3K isoforms in CHL patient samples demonstrated expression of the δ isoform in 81% of Reed-Sternberg cells, suggesting that this isoform may serve as a viable target in this disease[6]. Importantly, treatment of CHL cell lines with the PI3Kδ inhibitor idelalisib in a stromal cell co-culture resulted in a decrease in stroma-produced pAKT (thought to support CHL survival) and CHL derived CCL-5 (thought to promote stromal cell function). In addition to the tumor-microenvironment effects, PI3Kδ inhibition also directly induced cell cycle arrest and apoptosis within the CHL cells. We carried out a pilot trial evaluating PI3Kδ inhibition with idelalisib in 25 patients with relapsed/ refractory CHL[7]. These patients had received a median of 5 prior therapies and 92% had disease progression following brentuximab vedotin. Responses were initially observed in 3 of 24 response-evaluable patients (12.5%) and 17/24 (71%) showed decrease in disease burden. Longer follow up demonstrated an overall response rate of 20%[7]. These data indicate that single agent PI3Kδ targeting was tolerable and yields real, though modest response rates in CHL and sets the stage for further improvements of PI3K targeting in CHL. Since this trial was completed, additional data indicate that blockade of PI3Kδ directly inhibits MDSCs and Tregs, potentially further augmenting the immune response[4].

Combinations of PI3Kδ inhibition and PD1 blockade:

Umbralisib is a highly specific and orally available PI3Kδ inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma isoforms[8]. The PI3Ks are a family of enzymes involved in various cellular functions, including cell proliferation. survival, and differentiation, as well as intracellular trafficking and immunity[4,9]. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and is strongly upregulated and often mutated in various hematologic malignancies[10]. Inhibition of PI3Kδ signaling with umbralisib has demonstrated robust activity in both CLL and B cell lymphoproliferative disorders with a toxicity profile

that appears to be superior to idelalisib[11].

Importantly, a multi-center phase I/II trial evaluating umbralisib in combination with pembrolizumab (and anti-CD20 antibody ublituximab) for patients with relapsed/refractory CLL has been initiated. This study, which is open at our center has completed the dose escalation phase and has shown that full dose checkpoint inhibition (pembrolizumab 200 mg) can be safely combined with full dose umbralisib at 800mg/day[12]. The dose escalation portion tested two different doses of pembrolizumab (100 mg and 200 mg every 3 weeks). A dose limiting toxicity (DLT) was reached with pembrolizumab 200 mg dosing of elevated liver function tests. Therapy was interrupted, and the patient was re-challenged without re-occurrence of the abnormality. No maximum tolerate dose was reached, therefore pembrolizumab 200 mg was chosen as the dose to proceed in phase II studies.

Updated toxicity was presented in 2019[13]. Grade 3-4 transaminitis occurred in 4/20 (20%) of subjects. Other grade 3-4 non-immune related adverse events include neutropenia (40%), thrombocytopenia (15%), nausea (5%), and anemia (5%). Earlier data presented[12] showed other grade 3-4 events included rash, back pain, asthenia, elevated triglycerides, and hypophosphatemia.

Summary of Rationale and Background:

Treatment for relapsed CHL remains an unmet need. Targeting the microenvironment with PD1 blockade can yield responses in CHL, but the vast majority are partial responses and methods to augment the activity of anti-PD1 therapy are needed, but not known. PI3K isoforms including δ are overexpressed in CHL and preclinical data indicate that targeting these kinases can induce both direct antitumor effects as well as indirect efficacy via impacting the inflammatory microenvironment. Clinical data indicate that single agent targeting of PI3Kδ using idelalisib can yield tumor reduction in the majority of patients and objective responses in 20%. This study builds on both the data regarding PD1 and PI3K blockade in CHL to develop a safe combination regimen with these 2 classes of drugs.

3.0 DRUG INFORMATION

3.1 Pembrolizumab

Pembrolizumab must be obtained from commercial sources. Please refer to the current FDA-approved package inserts or prescribing information for information about possible side effects and instructions for preparation, handling, dosing and storage of pembrolizumab.

3.1.1 Adverse Reactions in >10% of Patients with Hodgkin Lymphoma treated with pembrolizumab (Merck&Co. Inc., 2017)

- **General Disorders and Administration Site Conditions**: Fatigue (26%; grade 3: 1%), pyrexia (24%; grade 3: 1%)
- **Respiratory, Thoracic and Mediastinal Disorders:** Cough (24%; grade 3: 0.5%), dyspnea (11%; grade 3: 1.0%)
- **Musculoskeletal and Connective Tissue Disorders**: Musculoskeletal pain (21%; grade 3: 1%), Arthralgia (10%; grade 3: 0.5%)
- **Gastrointestinal Disorders:** Nausea (13%; grade 3: 0%), diarrhea (20%; grade 3: 1.4%), vomiting (15%; grade 3: 0%)
- **Skin and Subcutaneous Tissue Disorders:** Pruritus (11%; grade 3: 0%), Rash (20%; grade 3: 0.5%)
- **Endocrine Disorders:** Hypothyroidism (14%; grade 3: 0.5%)
- **Infections and Infestations:** Upper respiratory tract infection (13%; grade 3: 0%)
- **Nervous System Disorders:** Headache (11%; grade 3: 0.5%), Peripheral neuropathy (10%; grade 3: 0%) Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥ 15% of Patients with Hodgkin Lymphoma
- Hypertransaminasemia (34%; Grade 3/4: 2%)
- Alkaline phosphatase increased (17%; grade 3/4: 0%)
- Creatinine increased (15%; grade 3/4: 0.5%)
- Anemia (30%; grade 3/4: 6%) • Thrombocytopenia (27%; grade 3/4:4%)
- Neutropenia (24%; grade 3/4: 7%)

Other clinically important adverse reactions that occurred in less than 10% of patients with CHL included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), myelitis and myocarditis (0.5% each).

Please refer to the FDA approved prescribing information for the most up to date information including warning and precautions (Merck&Co Inc., Prescribing Information; 2017)

3.2 Umbralisib

Classification: Dual inhibitor of Phosphatidylinositol-3-Kinase (PI3K) Delta and casein kinase 1 epsilon (CK1ε)
Formulation: See Investigator Brochure
Mode of Action: Irreversibly inhibits activity of the Class I Delta isoform of PI3K

How Supplied: 200 mg tablets

Storage: Store between 20°C and 25°C. Excursions permitted 15°C to 30°C. Do not freeze.

The Investigator's Brochure (IB) is the primary source for safety information. The umbralisib IB includes a summary of adverse event data and discussion on potential risks that have been observed or may be predicted to occur with this study drug. Refer to the most recent IB, which is updated periodically, for current information on umbralisib.

4.0 STAGING CRITERIA AND RISK STRATIFICATION

4.1 The Ann Arbor staging criteria will be utilized; Stage will be scored as maximal stage since diagnosis. This information will be reported with the results, but will not impact dosing or treatment duration.

4.2 Bulk will be defined as the long axis of the single largest nodal mass measuring > 10 cm. This information will be reported with the results, but will not impact dosing or treatment duration.

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

1. Relapsed or refractory CHL that has received at least 1 prior line of therapy.
2. Measurable FDG-avid disease defined by standard criteria (Lugano 2014)[14] and a minimum of 1.0 cm in diameter.
3. Prior treatment with anti-PD1 or anti-PDL1 therapy is allowed.
   a. Patients who are currently on anti-PD1 or anti-PDL1 therapy who have failed to achieve a CR after at least 18 weeks of treatment may enroll on study. For these patients, anti-PD1 or anti-PDL1 therapy may be delayed for screening and to align pembrolizumab dosing with the expected cycle 1 day 1. Patients with progressive disease after prior anti-PD1 or anti-PDL1 therapy do not have to be treated for 18 weeks.
4. ECOG performance status ≤ 2
5. Male or female ≥ 18 years of age
6. Ability to swallow and retain oral medication
7. Willingness and ability to comply with study and follow-up procedures, and give written informed consent
8. Female subjects of childbearing potential must be surgically sterile, be post-menopausal (for at least 1 year prior to screening visit), or must have a negative serum pregnancy test within 3 days prior to Cycle 1 Day 1 and agree to use medically acceptable contraception throughout the study period and for 4 months after the last dose of either study drug. Men of

reproductive potential may not participate unless they agree to use medically acceptable contraception throughout the study period and for 4 months after the last dose of either study drug. (See appendix 3 for further detail)

9. Patients must be expected to receive at least 2 cycles of therapy.
10. Patients should have a life expectancy if untreated of ≥90 days in the opinion of the investigator.
11. Patients must have a FDG-PET-CT of chest, abdomen, and pelvis within 42 days of enrollment.
12. Adequate organ system function, defined below:

    a. Absolute neutrophil count (ANC) > 750 / platelet count > 40,000
    b. Total bilirubin ≤1.5 times the upper limit of normal (ULN)
    c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN (if known liver involvement then ≤5 x ULN is allowed)
    d. Calculated creatinine clearance >30 mL/min (as calculated by the Cockcroft-Gault formula)

5.2 Exclusion Criteria

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

1. Patients receiving cancer therapy (i.e., chemotherapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization, prednisone > 10 mg or equivalent) or any investigational drug within 21 days of Cycle 1 Day 1. Patients receiving radiation therapy within 14 days from Cycle 1 Day 1. Anti-PD1 or anti-PDL1 therapy in patients with less than a CR after 18 weeks of such therapy is permitted to continue on schedule.
2. Discontinuation from prior anti-PD1 or anti-PDL1 therapy due to immune-related adverse event or any other treatment-related adverse event.
3. Autologous transplantation within 100 days.
4. Prior allogeneic transplant within 12 months of initiation on study.
5. Active GVHD within 90 days prior to Cycle 1 Day 1.
6. Evidence of active central nervous system lymphoma.
7. Pregnant or nursing women.
8. Evidence of chronic active Hepatitis B or chronic active Hepatitis C infection (HCV), active cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV IgG or CMV IgM is positive, the patient should be correspondingly evaluated for the presence of HBV DNA, HCV RNA or CMV DNA by PCR to determine presence or absence of active infection. If HBc antibody is positive, the subject must be evaluated for the presence of HBV DNA by PCR. If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by

PCR. Subjects with positive HBc antibody and negative HBV DNA by PCR are eligible. Subjects with positive HCV antibody and negative HCV RNA by PCR are eligible. Subjects who are CMV IgG or CMV IgM positive but who are CMV DNA negative by PCR are eligible.

9. Prior exposure to idelalisib (CAL-101), duvelisib (IPI-145), or any drug that specifically inhibits phosphoinositide-3-kinase (PI3K)
10. Evidence of ongoing active systemic bacterial, fungal or viral infection.
11. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    a. Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV)
    b. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of randomization
    c. Concomitant use of medication known to cause QT prolongation or torsades de pointes. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 3 months of randomization.
12. Patients with other prior malignancies except for adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, breast or cervical cancer in situ, or other cancer from which the patient has been disease-free for 5 years or greater, unless approved by the protocol principal investigator.
13. Patients with an active autoimmune disorder (with the exception of autoimmune hemolytic anemia, ITP or vitiligo).
14. History of non-infectious pneumonitis related to prior line of therapy.

6.0 REGISTRATION

6.1 Subjects must be registered prior to the start of protocol therapy. All of the eligibility requirements must have been met.

7.0 TREATMENT PLAN

7.1 For treatment or dose modification related questions, please contact Dr. Lynch (MedCon may also be used to contact MDs at 206-543-5300).

7.2 Administration of therapeutic agents: Each cycle of therapy is given every 21 days. Pembrolizumab is given on day 1 at a fixed dose of 200 mg IV per standard of care. Cycle start date may be +/-3 days from the prior cycle. Infusion details should be as per institutional standard of care.

All subjects will start umbralisib at 800 mg daily and this will be given continuously throughout the cycle on days 1-21 (see 7.2.1 for more information). Pembrolizumab will be continued for a total of 16 cycles on this study,

regardless of the number of cycles of previous treatment with pembrolizumab before entering the study. Patients may discontinue pembrolizumab early based on criteria listed in 7.4.5. Umbralisib will be continued indefinitely until disease progression or unacceptable toxicity. The order of administration is not specified in this trial. Further recommendations are listed in section 8.

7.2.1 Guidelines for administration of umbralisib

- Method of Administration: umbralisib will be administered orally once daily within 30 minutes of a meal
- Potential Drug Interactions: No drug Interactions have been reported to date.
- Prophylaxis: Subjects are required to start prophylaxis treatment with Pneumocystis jiroveci pneumonia (PCP) and antiviral therapy prior to cycle 1 day 1. Prophylaxis should continue throughout the duration of the subject's enrollment on study:
  - Anti-viral Prophylaxis: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent
  - PCP Prophylaxis: Trimethoprim/Sulfamethoxazole 160 mg/800 mg BID on Mondays/Tuesdays (or equivalent) or Dapsone 100 mg daily.
  - Final choice of PCP and antiviral prophylactic therapy is per investigator discretion
  - NOTE: If PCP or anti-viral therapy is not tolerated, alternate to a different PCP or anti-viral therapy, discontinue, or reduce dose/schedule as per investigator discretion.

7.2.2 Ordering umbralisib (TGR-1202): Umbralisib is available from TG Therapeutics. Please direct drug orders to ISTdrugorder@tgtxinc.com. The email should include the following: Requested quantity of TG Therapeutics study drug (umbralisib), date needed, Principal Investigator name, Study title, TG Therapeutics, Inc. tracking number (TGR-NTG-001), and Investigational drug pharmacy shipping address. Please allow 5 to 7 business days between drug ordering and drug arrival.

7.2.3 Dispensing of umbralisib: If any abnormality on the supplied bottles (umbralisib) is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact TG Therapeutics at productquality@tgtxinc.com.

Before dispensing, the site pharmacist must check that the umbralisib is in accordance with the product specifications and the validity is within the re-test date.

Subjects must be provided drug in its original container. Subjects should be instructed to return all empty bottles and any unused tablets when they return to the site. Study drug compliance should be reviewed with the patient at clinic visit and as needed. Missed doses will be documented in the subject's research record.

The exact dose and the date of missed doses of umbralisib must be recorded within the eCRF, subject's medical records, and/or in the drug accountability records. For the purpose of drug accountability and dosing, subjects should record the doses of umbralisib missed on a drug diary. Any error in drug administration should be recorded (e.g., missed dose). The pharmacist should follow the institution's SOP regarding drug accountability concerning the dispensation of umbralisib.

Umbralisib will be self-administered (by the patient). Tablets should be taken at approximately the same time each day within 30 minutes of a meal. Subjects should be instructed to swallow the tablets as a whole and should not chew or crush them.

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

7.3 Growth factor support: will be at the discretion of the treating team. Growth factors should be avoided whenever possible within 10 days of FDG-PET imaging. Antibiotic and antiemetic prophylaxis will be per institutional standard of care however PJP and anti-viral prophylaxis is recommended per standard of care, and it is required during treatment with umbralisib (see Section 7.2.1).

7.4 Criteria for removal from protocol treatment

7.4.1 Documented progression of disease by Lugano criteria (see appendix 3)[14]. Since anti-PD1 agents can be associated with tumor flare and mixed responses that may meet Lugano criteria for progression[15], subjects may continue treatment on protocol

beyond progression at the discretion of the investigator provided that the subject is clinically benefiting from the treatment. Examples of clinical benefit include but are not limited to overall decrease in tumor burden and improvement in symptoms.

7.4.2 If at any time the constraints of this protocol are detrimental to the subject's health and/or the subject no longer wishes to continue protocol therapy, protocol therapy shall be discontinued, the principal investigator shall be notified, and the reason for discontinuation shall be documented.

7.4.3 Delay of treatment for more than 8 weeks for either pembrolizumab or umbralisib due to related adverse events unless prophylactic measures can be taken for subsequent cycles. Treatment delays of greater than 8 weeks are permitted at investigator discretion and with notification of TG Therapeutics. If only one agent is discontinued, the other agent should be continued provided that at least one of the following criteria is met.

- The subject has received at least 6 cycles of therapy.
- Achieved a FDG-PET-defined CR

7.4.4 The subject may withdraw from the treatment at any time for any reason.

7.4.5 Subjects may opt to discontinue pembrolizumab prior to completing 16 cycles of treatment and continue receiving umbralisib if they have one of following

- Achieved a FDG-PET-defined CR
- Received a minimum of 6 additional doses of pembrolizumab after achieving a PR.

7.5 Study stopping rules for immune-related toxicity

There is the potential for increased immune-related adverse events with combination of umbralisib and pembrolizumab. The study will be suspended and an ad hoc safety committee will be convened with individuals with appropriate expertise (majority of whom are no directly affiliated with the study) for consideration of results and appropriate modification or termination of the study if there is

sufficient evidence that the probability of Grade 3 or 4 immune-related adverse events that do not resolve to Grade ≤ 2 within 72 hours exceeds 20%. This will be deemed to occur if the lower level of a one-sided 80% confidence interval for this proportion exceeds 20%.

The protocol was originally written to determine if there was sufficient evidence that the probability of grade 3-4 immune-related adverse events exceeded 10%. This was based on earlier data, though follow up data from a study that combined umbralisib with pembrolizumab and a CD20 monoclonal antibody found 4/20 (20%) subjects had grade 3-4 transaminitis. This protocol hit the suspension rule when 2 out of the first 5 subjects met this (grade 3 rash and grade 3 ALT elevation).

An ad hoc safety committee was convened. Since there are no standard therapies beyond PD1 inhibitors in the treatment of classical Hodgkin lymphoma, it was felt that a higher threshold for toxicity was warranted. Therefore, the threshold was increased to suspend again if the lower level of a one-sided 80% confidence interval for this proportion exceeds 20% (increased from 10%)

In addition, a change was recommended to allow for prednisone treatment that exceeds 10 mg for 6 weeks before requiring discontinuation of the protocol.

There are 15 subjects remaining in the study to be enrolled. The study operation rules will include the first two subjects as meeting this criteria, and will mandate another suspension in the following circumstances

- If 4 out of the first 11 or fewer patients, or 5 out of the first 15 or fewer, or 6 out of 20 or fewer patients experience Grade 3 or 4 immune-related adverse events that do not resolve to Grade ≤ 2 within 72 hours.

8.0 DOSAGE MODIFICATION, DELAY, OR DISCONTINUATION

8.1 Dose modification of pembrolizumab

8.1.1 Withholding pembrolizumab: Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment (see below). The use of corticosteroids should be considered for management of immune-related adverse events (irAEs). Please refer to prescriber

manual for further detail on dosing of corticosteroids for pembrolizumab-related toxicity. If the drug-related toxicity does not resolve to Grade 0-1 within 4 weeks after onset of toxicity, discontinuation is recommended. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per the below criteria (may resume upon recovery to grade 0 or 1 toxicity unless otherwise noted below).

- Hematological toxicity- Grade 4; Pembrolizumab should be held until resolved to Grade ≤ 3.
- Colitis, any Grade– Grade 2-3; also administer high-dose systemic corticosteroids (followed by a taper).
- Hyperthyroidism– Grade 3; administer high-dose systemic corticosteroids (followed by a taper).
- Hypophysitis– Grade 2-4; administer high-dose systemic corticosteroids (followed by a taper).
- Nephritis– Grade 2; consider administration high-dose systemic corticosteroids (followed by a taper).
- Pneumonitis– Grade 1-2; administer high-dose systemic corticosteroids (followed by a taper). Pembrolizumab may be resumed after resolution.
- Hepatitis- Grade 2-3. Pembrolizumab should be held until resolution to Grade ≤ 1. If the subject has baseline liver involvement and Grade 2 abnormalities at baseline, treatment may continue unless it worsens to Grade 3.
- Other treatment-related toxicity, severe or Grade 3; may require high-dose systemic corticosteroids (based on severity). Upon improvement to grade 0 or 1, initiate corticosteroid taper and continue to taper over at least 1 month. Restart pembrolizumab if the adverse reaction remains at grade 0 or 1 and steroid dose is ≤ 10 mg. Please refer to the FDA approved pembrolizumab prescribing information for more information.

8.1.2 Discontinuing Pembrolizumab: If any of the following criteria are met, pembrolizumab should be permanently discontinued

- Confirmed radiographic disease progression per the appropriate tumor evaluation criteria.
- Immune-mediated Pneumonitis – discontinue for Grade 3-4 or recurrent Grade 1-2 pneumonitis

- Colitis – Grade 4
- Immune-mediated Hepatitis – Grade 4
- Immune-mediated Endocrinopathies – (excluding endocrinopathies controlled with hormone replacement therapy)
    - Hyperthyroidism – Grade 4
- Immune-mediated Nephritis – Grade 3-4
- Infusion-related reaction – Grade 3 or 4
- Inability to reduce corticosteroid dose to 10mg or less of prednisone or equivalent per day within 6 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 4 weeks after last dose of pembrolizumab
- Any Grade 3-4 treatment-related adverse reaction that recurs
- Please refer to the FDA approved pembrolizumab prescribing information for more information.
- For treatment or dose modification related questions, please contact Dr. Lynch (MedCon may also be used to contact MDs at 206-543-5300).

8.2 Umbralisib dose reduction steps: If a subject undergoes a dose reduction, it should not be subsequently increased, even if the toxicity resolves to Grade 0. However, if further evaluation of the toxicity reveals the event was not related to umbralisib, this should be recorded in the medical record and dose re-escalation to the previous dose may be considered at the discretion of the investigator.

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

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities.

NCI-CTCAE Grade	Umbralisib Dose Delay or modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 2 neutropenia	Maintain current umbralisib dose. Consider supportive care as warranted.
Grade 3 neutropenia	Maintain current umbralisib dose for first occurrence, consider supportive care. If recurrence or persistent Grade 3 after re-challenge, resume umbralisib at next lower dose level at discretion of the principal investigator/sub-investigator.
Grade 4 neutropenia or occurrence of neutropenic fever/infection	Delay umbralisib until Grade ≤ 3 and/or neutropenic fever or infection is resolved; thereafter, resume at current dose. Consider supportive care. If recurrence after re-challenge, resume umbralisib at next lower dose level at discretion of the principal investigator/sub-investigator.
Thrombocytopenia	
Grade ≤ 3 thrombocytopenia	Maintain current umbralisib dose level and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay umbralisib until Grade ≤ 3; thereafter, resume at current dose. Consider supportive care intervention as warranted. If recurrence after re-challenge, resume umbralisib at next lower dose level at discretion of the principal investigator/sub-investigator.
Hepatitis	
Grade 2-3 AST/ALT or total bilirubin increase	Delay umbralisib until resolution to Grade ≤ 1. If the subject has baseline liver involvement and grade 2 abnormalities at baseline, treatment may continue unless it worsens to grade 3. For grade 3 toxicity, reduce the umbralisib dose to the next lower dose level upon resolution to Grade ≤ 1.
Grade 4 AST/ALT or total bilirubin increase	Permanently discontinue umbralisib.
Immune related pneumonitis*	
Grade 1-2	Stop all therapy (umbralisib and pembrolizumab) and hold until complete resolution. Restart umbralisib at one lower dose level. Restart pembrolizumab at current dose. If recurrence after re-challenge, discontinue all treatment therapy.
Grade ≥ 3	Discontinue all therapy (umbralisib and pembrolizumab).
* For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at investigator's discretion. While pneumonitis has been minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis must be instituted as outlined in 7.2.1.	

Diarrhea and/or colitis	
Diarrhea grade ≤ 2	Maintain current umbralisib dose level if tolerable or hold and then resume at current dose level once has resolved. NOTE: If persistent grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ grade 1. If recurrence after re-challenge, resume umbralisib at current dose or next lower dose level at discretion of the principal investigator/sub-investigator.
Diarrhea ≥ 3	Withhold umbralisib until Grade ≤ 1. Resume umbralisib at current dose or next lower dose level as per discretion of principal investigator/sub-investigator. If recurrence after rechallenge, resume umbralisib at next lower dose level at discretion of the principal investigator/sub-investigator.
Colitis (all grades)	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level
All other non-hematological events	
Grade ≤ 2	Maintain current umbralisib dose level.
Grade ≥ 3	Withhold umbralisib until Grade ≤ 1. If recurrence after re-challenge, resume umbralisib at current dose or next lower dose level at the discretion of the principal investigator/sub-investigator.

8.3 Concomitant Therapy

Medications used during the course of the study will be documented.

8.3.1 Prohibited Concomitant Therapy: The administration of concurrent medications intended to treat the primary cancer are not allowed during protocol therapy. This includes any chemotherapy, investigational agent, biologic agent or other anti-tumor agents. Radiation therapy is also prohibited.

8.3.2 Subjects should be strongly discouraged from taking any “alternative” or “naturopathic” medications since these agents may interfere with metabolism of study medications.

9.0 STUDY CALENDAR

Required Studies	Screening	Cycle 1-4 Day 1	Cycle 1-4 Day 8	Restaging[5]	Cycle 5-16 day 1	Within 3 days prior to every 4th cycle starting with cycle 17 while on umbralisib alone	End of treatment[7]	Follow-up[6]
Scheduling window (days)	-42 to -1[9]	+/- 3 days	+/- 2 days		+/- 3 days			
Physical								
History and Physical	X	X[1]			X[3]	X	X	
Performance Status	X	X[1]			X[3]	X	X	
Clinical Disease Assessment	X	X[1]			X[3]	X	X[7]	X
Adverse Event Assessment	X	X[1]			X[3]	X	X	
Concomitant Medication Assessment	X	X			X	X	X	
Lab[2]								
TSH, T3, T4, LDH, ESR[2]	X			X		X	X	
CBC with differential	X	X[1]	X	X	X	X	X	
Comprehensive metabolic panel	X	X[1]	X	X	X	X	X	
Serum pregnancy test[4]	X[4]							
Hepatitis B/C serology, direct and indirect coombs, CMV	X							
CMV surveillance by PCR[10]		X[10]			X[10]	X[10]	X[10]	
Radiology								
EKG	X							
PET/CT[5]	X			X			X[7]	
CT[5]				X				
Correlative Studies[8]	X	X		X	X			

1. For Cycle 1 Day 1, pre-entry H&P, performance status, disease assessment and adverse event assessment may be used (these do not need to be repeated within 3 days) and labs done within 14 days of cycle 1 day 1 are acceptable.
2. LDH and ESR must be done within 14 days prior to study entry.
3. Between cycles 6-16 history, physical, performance status, and AE assessment by the investigator/sub-investigator may be performed every 2 cycles at investigator discretion.
4. Serum pregnancy test in women of childbearing potential should be performed with screening and repeated within 3 days of cycle 1 day 1.
5. FDG-PET-CT should be performed at baseline within 42 days prior to first dose of cycle 1. Diagnostic quality CT is not required at baseline for subjects who have CT measurable lesions from CT component of FDG-PET-CT. Follow up CT-scans should be performed after day 1 of cycle 3, 6, 9, 12 and 16, but prior to day 1 of the next cycle. PET-CT should be performed on the next imaging assessment for: 1) subjects meeting CR criteria by CT, 2) subjects meeting criteria for PR on 2 consecutive images, 3) subjects being removed from protocol for reasons other than progressive disease (including end of treatment), and 4) at the discretion of the investigator. For patients continuing on umbralisib for cycle 17 and beyond, imaging should be performed at the discretion of the investigator and upon clinical suspicion of progression/relapse.
6. Subjects continuing on umbralisib alone for cycle 17 and beyond should be seen in clinic every 4th cycle (Cycle 17, cycle 21, cycle 25 etc.).
7. There should be an end of treatment visit within 28 days after completion of therapy. For patients ending treatment on study for reasons other than progression, end of treatment imaging is strongly recommended within 28 days of completion of therapy. Imaging within this window can be recorded for a final response assessment. All subjects will be followed for survival and remission status while on treatment and up to 1 year after end of treatment visit.
8. Correlative studies will be carried out whenever possible and include PD1/PDL1/PDL2 expression, MRD (e.g. Adaptive Clonoseq or similar) and cytokine monitoring. This will include up to 10 unstained slides of diagnostic tissue block from most recent biopsy (additional biopsy not required for study entry),as well as whole blood for plasma (20 ml EDTA or equivalent) at baseline and after cycle 2, at end of 16 cycles or progression (whichever comes first), as well as any time point that a PET scan is being performed for response assessment
9. Testing can be performed within 42 days of cycle 1 day 1 unless specifically indicated above.
10. CMV screening by PCR within 3 days prior to cycles 4, 7, 10, 13 and 17, and then within 3 days prior to every 4th treatment cycle thereafter for all subjects receiving study treatment. A final CMV test by PCR should be done upon treatment discontinuation.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Definitions of Disease, Criteria for Evaluation and Endpoint Definitions – response will be defined by standard NCI criteria (Lugano 2014) for lymphoid malignancies.

11.0 STATISTICAL CONSIDERATIONS

11.1 The primary objective of this study is to estimate the CR rate of this regimen. In a population of CHL patients who have failed after autologous transplant, the CR rate of single agent pembrolizumab is 16%[2]. Targeted accrual is 20 subjects. If the assumed-true CR is 40%, we will have 88% power to observe a statistically significantly higher CR than the fixed rate of 16% with 20 subjects (at the one-sided significance level of 0.1). The 95% confidence interval (CI) by exact Clopper Pearson for the proposed 40% CR is from 19% to 64%, which will reasonable exclude a response rate of < 16%. With 20 subjects, CI will change to 27% to 73% with estimated CR 50%, and 36% to 81% with estimated CR 60%

11.2 Anticipated accrual: We anticipate accrual of 20 subjects over 2 years.

11.3 Descriptive summary statistics for continuous variables will include sample size, mean, standard deviation (SD), median, minimum and maximum for both baseline and post-baseline measurements (if applicable). Summary statistics for categorical variables will include sample size, frequency and percentages.

11.4 Estimated distribution of study population by gender and race and ethnicity:

Ethnic Category	Females	Males	Total
American Indian/Alaska Native			
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	7	10	17
More than one race	0	0	0
Unknown or not reported	0	0	0
Racial Categories: Total of all subjects	8	12	20

12.0 STUDY MONITORING AND REPORTING PROCEDURES

12.1 Adverse Event Reporting

Reporting of AEs and SAEs should commence after first administration of either umbralisib or pembrolizumab, and should continue for up to 30 days after

last dose of study treatment (pembrolizumab or umbralisib, whichever is given last).
Complete and timely reporting of adverse events (AEs) is required to ensure the safety of subjects. Reporting requirements are determined by the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event. The guidelines outlined in this section, as well as the specific direction on each report form must be followed. The NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE) will be used to classify and grade toxicities. The CTC can be found on the Cancer Therapy Evaluation Program (CTEP) homepage at
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

12.2 Definitions and descriptions of terms used in adverse event reporting.

Adverse Event (AE)
An *adverse event (AE)* is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure. The investigator should log AEs that are deemed to be clinically significant and assess their attribution to either or both of the study medications.

Serious Adverse Event or Adverse Drug Reaction
A *Serious Adverse Event (SAE)* or *Adverse Drug Reaction* (ADR) means any AE/ADR occurring at any dose that results in:

- Death;
- A life-threatening AE/ADR (i.e, the patient/subject was, in the view of the initial reporter/investigator, at immediate risk of death from the AE as it occurred. It does not refer to an AE that hypothetically might have caused death if more severe);
- Inpatient hospitalization or prolongation of existing hospitalization (i.e, hospitalization was required to treat or diagnose the AE/ADR: excludes hospitalization for unrelated reasons);
- A persistent or significant disability or incapacity (disability here means that there is a substantial disruption of a person's ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event (i.e., AEs/ADRs that might not be immediately life-threatening, or result in death or hospitalization might be considered serious when, based upon appropriate medical and scientific judgment, they might jeopardize the patient/subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed above);

- Any suspected transmission via a medicinal product of an infectious agent.

Grade

Grade is defined as the severity of the adverse event. The CTCAE Version 5.0 must be used to determine the grade of the adverse event. If toxicity is not listed in the CTCAE use the following general criteria for grading.

0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

Attribution

Attribution is defined as the determination of whether an adverse event is related to a medical treatment or procedure. The investigator or authorized sub-investigator will assess attribution according to the following categories:

- *Unrelated:* the adverse event is *clearly NOT related* to therapy
- *Unlikely:* the adverse event is *doubtfully related* to therapy
- *Possible:* the adverse event *may be related* to therapy
- *Probable:* the adverse event is *likely related* to therapy
- *Definite:* the adverse event is *clearly related* to therapy

Unexpected Adverse Event

An *unexpected adverse event* is any adverse event that is not listed in the current Investigator's Brochure, package insert, protocol, or associated documents; or the specificity or severity of which is not consistent with these documents.

12.3 Routine Reporting

Routine reporting is required for all grade adverse events. Routine reports include data after each cycle of therapy and 30 days after the last dose of study drugs, or until the patient receives an alternative anti-cancer therapy, whichever date comes first.

12.4 Expedited Reporting –

SAE Reporting to TG Therapeutics

SAEs require expeditious handling and reporting to TG Therapeutics in order to comply with regulatory requirements. All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to TG Therapeutics at safety@tgtxinc.com (copy

mcoon@tgtxinc.com and donna.gesumaria@tgtxinc.com) within 24 hours of the first knowledge of the event by physician member of the research team or research personnel on an SAE Form (MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable). Include the TG Therapeutics, Inc. tracking number (TGR-NTG-001) on the SAE report.

SAE Reporting to Regulatory Agencies

Sponsor-Investigator is responsible for reporting serious, unexpected, suspected adverse reactions (SUSARs) to the FDA in accordance with regulations under 21 CFR 312.32. Sponsor-Investigator is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the FDA within 7 calendar days after being notified of the event. Sponsor-Investigator will report other SUSARs to the FDA by a written safety report within 15 calendar days of notification. Other SAEs will be reported to the FDA on an annual basis.

The investigator must report SAEs and follow-up information to the responsible Institutional Review Board (IRB) according to the policies of the IRB.

The following are events of special interest, and will need to be reported within 2 business days of awareness by a member of the study team with exceptions as indicated below for reporting these events to TG Therapeutics within 24 hours of awareness:

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

During the course of the study, all female subjects of childbearing potential must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a subject 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 subject may be pregnant after the subject has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must submit a Pregnancy Report Form to TG Therapeutics within 24 hours of the first knowledge of the event by the treating physician or research personnel. Abortions (spontaneous, accidental, or therapeutic) must also be reported to TG

Therapeutics within 24 hours of awareness using the Pregnancy Report Form. Submit Pregnancy Report Forms to TG Therapeutics, Inc. following the same process described for reporting SAEs to TG Therapeutics, Inc. (to safety@tgtxinc.com, mcoon@tgtxinc.com and donna.gesumaria@tgtxinc.com, and including the TG Therapeutics, Inc. tracking number (TGR-NTG-001) on the Pregnancy Report Form).

Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be expeditiously reported as an SAE to TG Therapeutics within 24 hours of the first knowledge of the event by the treating physician or research personnel following the same process described for reporting SAEs to TG Therapeutics, Inc.

In the event a subject's partner becomes pregnant, a Pregnancy Report Form should be completed and submitted to TG Therapeutics following the same process described for reporting SAEs to TG Therapeutics, Inc., and the partner will be requested to consent to access to medical records. After the subject's partner provides consent, the pregnant partner and baby will be followed to see what effect the drug(s) under study may have on the outcome of the pregnancy or the health of the newborn.

See APPENDIX 3: CONTRACEPTIVE GUIDELINES AND PREGNANCY for additional information.

Study Drug Overdose

Any accidental or intentional overdose with the study treatment (either umbralisib or pembrolizumab) that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to TG Therapeutics immediately (within 24 hours of awareness) on an SAE form and following the same process described for SAEs. If a study drug overdose occurs, subjects should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

12.5 Data Safety and Monitoring Plan-

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutchinson Cancer Research Center (FHCRC) Scientific Review Committee (SRC) and the FHCRC Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

12.6 **Required Records and Materials**

12.6.1 Original signed informed consent form will be kept with the study coordinating office. A copy will be kept in the patient's clinical chart..

12.6.2 Data will be collected on patient characteristics, disease characteristics, protocol therapy, response to treatment, adverse events and follow-up for relapse and survival. Source documentation may include the subject's medical record from SCCA/UWMC and/or outside providers which would include history and physical exams, documentation of protocol therapy, labs, scans, x-rays, hospitalizations, operative reports, pathology reports etc.

13.0 ELEMENTS OF INFORMED CONSENT

All Institutional, NCI, State and Federal regulations concerning informed consent and peer judgment will be fulfilled. Written consent will be obtained from all subjects entering the study.

14.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

14.1 Study Site Training

Before initiation of the study, the PI, or its designated representatives will review and discuss the following items with the Investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, and the ability of the site to satisfactorily complete the protocol.

14.2 Informed Consent

The PI/sub-investigator assumes the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or parents/legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the Sponsor or designee and approved by the IRB prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

14.3 Institutional Review Board

The PI will assure that an appropriately constituted IRB that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB for its review and approval. A photocopy of the IRB notification of approval must be forwarded to the Sponsor or its designee before any investigational supplies will be shipped to the PI.

The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB, and that no changes will be made to the protocol without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

The Investigator or designee will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

14.4 Subject Privacy

The investigators affirm and uphold the principle of the subject's right to privacy. The investigator shall comply with applicable national and local privacy laws.

15.0 REFERENCES:

1. Ansell SM, Lesokhin AM, Borrello I, et al: PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372:311-9, 2015
2. Armand P, Shipp MA, Ribrag V, et al: Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. J Clin Oncol, 2016
3. Gopal AK, Chen R, Smith SE, et al: Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood 125:1236-43, 2015
4. Ali K, Soond DR, Pineiro R, et al: Inactivation of PI(3)K p110delta breaks regulatory T-cell-mediated immune tolerance to cancer. Nature 510:407-11, 2014
5. Greaves P, Clear A, Owen A, et al: Defining characteristics of classical Hodgkin lymphoma microenvironment T-helper cells. Blood 122:2856-63, 2013
6. Meadows SA, Vega F, Kashishian A, et al: PI3Kdelta inhibitor, GS-1101 (CAL-101), attenuates pathway signaling, induces apoptosis, and overcomes signals from the microenvironment in cellular models of Hodgkin lymphoma. Blood 119:1897-900, 2012
7. Gopal AK, Fanale MA, Moskowitz CH, et al: Phase II study of idelalisib, a selective inhibitor of PI3Kdelta, for relapsed/refractory classical Hodgkin lymphoma. Ann Oncol 28:1057-1063, 2017
8. Burris HA, Patel MR, Brander DM, et al: TGR-1202, a Novel Once Daily PI3Kδ Inhibitor, Demonstrates Clinical Activity with a Favorable Safety Profile, Lacking Hepatotoxicity, in Patients with Chronic Lymphocytic Leukemia and B-Cell Lymphoma. Blood 124:1984-1984, 2014
9. Brown JR: The PI3K pathway: clinical inhibition in chronic lymphocytic leukemia. Semin Oncol 43:260-4, 2016
10. Burris HA, Patel MR, Fenske TS, et al: Clinical activity and safety profile of TGR-1202, a novel once daily PI3Kδ inhibitor, in patients with CLL and B-cell lymphoma. Journal of Clinical Oncology 33:7069-7069, 2015
11. Davids MS, Flinn IW, Mato AR, et al: An Integrated Safety Analysis of the Next Generation PI3Kδ Inhibitor Umbralisib (TGR-1202) in Patients with Relapsed/Refractory Lymphoid Malignancies. Blood 130:4037-4037, 2017
12. Mato AR, Dorsey C, Chatburn ET, et al: Phase I/II Study of Pembrolizumab in Combination with Ublituximab (TG-1101) and Umbralisib (TGR-1202) in Patients with Relapsed/Refractory CLL. Blood 130:3010-3010, 2017

13. Mato AR, Svoboda J, Luning Prak ET, et al: PHASE I/II STUDY OF UMBRALISIB (TGR-1202) IN COMBINATION WITH UBLITUXIMAB (TG-1101) AND PEMBROLIZUMAB IN PATIENTS WITH REL/REF CLL AND RICHTER'S TRANSFORMATION. Hematological Oncology 37:119-120, 2019

14. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014

15. Cheson BD, Ansell S, Schwartz L, et al: Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy. Blood, 2016

16.0 Appendices

Appendix 1: ECOG 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 (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Response Criteria: "The Lugano Classification"[14]

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

Response and Site	**PET-CT–Based Response**	CT-Based Response
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met

Response and Site	**PET-CT–Based Response**	CT-Based Response
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

- ↵* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

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

Appendix 3: 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 4 months after stopping treatment. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomised male partner should be the sole partner for that patient.
4. Oral contraception, injected or implanted hormonal methods.
5. Use of a combination of any two of the following (a+b):
    a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

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

- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Women of child-bearing potential must have a negative serum pregnancy test ≤ 3 days prior to initiating treatment.

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment and for 4 months after study drug discontinuation and should not father a child in this period. Sperm donation is also prohibited until 4 months after study discontinuation.

If a partner of a participant were to become pregnant, a pregnant partner consent will be created and the partner's and/or child's medical records will be followed for 3 months after the termination of the pregnancy to determine outcome including voluntary or spontaneous termination, details of the birth and the presence or absence of any birth defects, congenital abnormalities or maternal and/or newborn complications.

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