



## Protocol Abstract Page

### Phase II study of TAK-228 in Relapsed Lymphoma 2014-0501

#### Core Protocol Information

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#### Abstract

##### Objectives:

##### Primary Objectives

##### Phase II:

The primary objective of the Phase II portion of the trial is to define the overall response rate, defined as the combination of complete (CR) and partial (PR) response rates, of TAK228 in patients with relapsed lymphoma.

##### Secondary Objectives

##### Phase II:

The secondary objectives of the Phase II portion of the trial are to define the safety & tolerability, progression free survival, duration of response, and overall survival of TAK228 in patients with relapsed lymphoma.

##### Exploratory Objectives

The exploratory objectives are to define:

- Determination of response associated clinical characteristics,
- The incidence of activating mutations in MTOR and related genes in patients who respond to TAK228 in their archival lymphoma biopsy tissue,
- The change in phosphorylation of mTORC1/2 target proteins and related signaling proteins at baseline and after therapy with TAK228 in peripheral blood mononuclear cells by utilizing reverse phase protein array,
- The change in phosphorylation of mTORC1/2 target proteins and related signaling proteins at baseline and after therapy with TAK228 in optional pre- and post- therapy biopsy by utilizing reverse phase protein array

##### Rationale: (Be as concise as possible)

The mTOR pathway is an active target in multiple lymphoma subtypes. mTOR activity has been shown to be increased in nearly all lymphoma subtypes, including diffuse large B cell, mantle cell, and Hodgkin

lymphomas. The rapalog mTOR inhibitors (Temsirolimus and Everolimus) directly effect mTORC1 and have demonstrated promising efficacy in multiple lymphoma subtypes.

Temsirolimus is approved in Europe for mantle cell lymphoma, and has shown promising responses in diffuse large b-cell, follicular, and other indolent lymphomas. Everolimus has also shown promising responses in relapsed aggressive lymphoma. In addition, Everolimus has shown impressive response in relapsed/refractory Hodgkin lymphoma.

It is now known that inhibition of mTORC1, although effective for a portion of patients with lymphoma, leads to transient benefit at best, and perhaps even tumor growth for some cancers. Demonstrating the complexity of the crosstalk found in this pathway, mTORC1 inhibition can lead to activation of the PI3K pathway due to mTORC2 negative feedback, resulting in phosphorylation of Akt.

We believe inhibition of both mTORC1 and mTORC2 with TAK228 may result in a significant improvement in the efficacy seen to date with mTORC1 inhibitors in lymphomas. This clinical trial is based on: 1) the known promising activity of mTORC1 inhibitors in various subtypes of lymphomas, 2) the known escape/resistance mechanism that cancer utilizes to overcome mTORC1 inhibitor via mTORC2 stimulation of Akt, and 3) the early signal of excellent tolerance and efficacy of TAK228 in clinical trials thus far.

It is our hypothesis that TAK228 will result in response rates higher than previously seen with rapalogs, with acceptable tolerability. The goal of our trial is to identify lymphoma subtypes with high response rates for future clinical trials, either combined with current standard therapies or with novel targeted agents.

It is currently difficult to predict which patients will have response to mTOR pathway directed therapies due to lack of actionable biomarkers. It is possible to assess for the activity of mTOR inhibition by evaluation of phosphorylation of downstream targets of mTOR, such as S6K and 4EBP1. To evaluate the baseline phosphorylation and effect of TAK228 on these markers, we propose to collect peripheral blood mononuclear cells and archival tissue blocks from patients enrolled on trial for correlative studies. The peripheral blood mononuclear cells will be evaluated as a surrogate for mTORC1/2 inhibition and Akt phosphorylation after exposure to TAK228 via reverse phase protein array (RPPA). For the list of the 217 currently utilized antibodies in the MD Anderson RPPA platform. Archival tumor blocks will be stored for attempted correlation of clinical responders vs non-responders with genomic assessment.

It has recently been reported that mutations of the MTOR may activate the pathway and thus predict clinical response to mTOR inhibitors. Patients with available archival tissue will undergo an evaluation for the presence of an MTOR mutation which could serve as a potential biomarker in future clinical trials.

### **Eligibility: (List All Criteria)**

#### **Inclusion:**

- 1) Each patient must meet all of the following inclusion criteria to be enrolled in the study: 1. Male or female patients 18 years or older.
- 2) Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
- 3) Female patients who: are postmenopausal for at least 1 year before the screening visit, OR are surgically sterile, OR if they are of childbearing potential, agree to practice 1 effective methods of contraception and one additional effective (barrier) method, at the same time, from the time of signing the informed consent through 90 days (or longer, as mandated by local labeling [eg, USPI, SmPC, etc;]) after the last dose of study drug, or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence [e.g, calendar, ovulation, symptothermal, postovulation

methods] and withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.

4) Male patients, even if surgically sterilized (ie, status post-vasectomy), who: agree to practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence [e.g, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together; Agree not to donate sperm during the course of this study or 120 days after receiving their last dose of study drug

5) Patients must have a diagnosis of prior treated diffuse large b-cell lymphoma, mantle cell lymphoma, transformed lymphoma, follicular lymphoma (any grade), small lymphocytic lymphoma, marginal zone lymphoma, or Hodgkin lymphoma with at least 2 lines of therapy without a curative treatment options.

6) Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status  $\leq 2$ .

7) Adequate organ function, as specified below, within 3 weeks before the first dose of study drug: a) Bone marrow reserve consistent with: absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$ ; platelet count  $\geq 100 \times 10^9/L$ ; hemoglobin  $\geq 9$  g/dL without transfusion within 1 week preceding study drug administration; b) Hepatic: total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN), transaminases (aspartate aminotransferase-AST and alanine aminotransferase ALT)  $\leq 2.5 \times$  ULN ( $\leq 5 \times$  ULN if liver metastases are present); c) Renal: creatinine clearance  $\geq 50$  mL/min based either on Cockcroft-Gault estimate or based on urine collection (12 or 24 hour); d) Metabolic: fasting serum glucose ( $\leq 130$  mg/dL) and fasting triglycerides  $\leq 300$  mg/dL;

8) Ability to swallow oral medications;

9) Measurable disease, defined as  $\geq 1.5$  cm on imaging assessment.

#### **Exclusion:**

1) Eligible for therapy for the lymphoid malignancy which has a high likelihood of a curative result in the opinion of the investigator.

2) Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period

3) Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol

4) Concurrent malignancies except basal or squamous cell carcinoma of the skin, or cervical carcinoma in situ treated with curative intent. Any cancer from which the patient has been disease free for at least 2 years is permissible.

5) Treatment with any investigational products within 14 days before the first dose of study drug

6) Failed to recover to baseline or stable grade 1 from the reversible effects of prior anticancer therapies with the exception of alopecia.

7) Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of TAK228; such as significant chronic diarrhea. In addition, patients with enteric stomata are also excluded.

- 8) Poorly controlled diabetes mellitus defined as HbA1c > 7%; subjects with a history of transient glucose intolerance due to corticosteroid administration are allowed in this study if all other inclusion/exclusion criteria are met;
- 9) History of any of the following within the last 6 months prior to study entry: ischemic myocardial event, including angina requiring therapy and artery revascularization procedures; Ischemic cerebrovascular event, including TIA and artery revascularization procedures; Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia); Placement of a pacemaker for control of rhythm; New York Heart Association (NYHA) Class III or IV heart failure; Pulmonary embolism.
- 10) History of any of the following within the last 6 months prior to study entry: Requirement of inotropic support; Serious uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia); Placement of a pacemaker for control of rhythm
- 11) Significant active cardiovascular or pulmonary disease at the time of study entry, including: uncontrolled high blood pressure (i.e., systolic blood pressure >180 mm Hg, diastolic blood pressure > 95 mm Hg) Use of anti-hypertensive agents to control hypertension before cycle 1 day 1 is allowed; Pulmonary hypertension; Uncontrolled asthma or O2 saturation < 90% by ABG (Arterial Blood Gas) analysis or pulse oximetry on room air; Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement; medically significant (symptomatic) bradycardia; History of arrhythmia requiring an implantable cardiac defibrillator; Baseline prolongation of the rate-corrected QT interval (QTc) (e.g., repeated demonstration of QTc interval > 480 milliseconds, or history of congenital long QT syndrome, or torsades de pointes).
- 12) Treatment with strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, CYP2C9 or CYP2C19 within 1 week preceding the first dose of study drug.
- 13) Patients receiving systemic corticosteroids (either IV or oral steroids, excluding inhalers or low-dose hormone replacement therapy as defined no greater than 20mg of prednisone daily) within 1 week before administration of the first dose of study drug.
- 14) Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise participation of the patient in the study.
- 15) Central nervous system (CNS) lymphoma.
- 16) Known human immunodeficiency virus infection.
- 17) Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
- 18) Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection
- 19) Daily or chronic use of a proton pump inhibitor (PPI) and/or having taken a PPI within 7 days before receiving the first dose of study drug

**Are patients <18 years of age eligible to participate in this study?**  Yes  No

**Studies that include children must meet the criteria for inclusion.**

[http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1\\_05\\_NIH-Inclusion%20of%20Children.doc](http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc)  
<http://www.hhs.gov/ohrp/policy/populations/children.html>

**Studies that exclude children must have appropriate justification. Please select all that apply:**

Phase I or Phase II study targeting cancer that is very unusual in pediatrics (e.g., prostate, lung, breast, chronic lymphocytic leukemia, etc.)

Are participants >65 years of age eligible to participate in this study?  Yes  No

Are pregnant women eligible to participate in this study?  Yes  No

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?

Yes  No

**Disease Group:**

Lymphoma

**Treatment Agents/Devices/Interventions:**

TAK228

**Proposed Treatment/Study Plan:**

Is treatment assignment randomized?  Yes  No

Is this a blinded or double-blinded study?  Yes  No

TAK228 milled API will be administered once daily at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. It is recommended that each dose of TAK228 be given orally with 8 ounces (240 mL) of water. TAK228 should be administered on an empty stomach, and patients should be instructed to refrain from eating or drinking (aside from water and prescribed medications) for 2 hours before and 1 hour after each dose. Cycles are repeated every 28 days.

### **Screening Evaluation**

A history and physical examination, including performance status evaluation, height, weight, and vital signs, should be performed within 28 days prior to the first dose of TAK228.

The following laboratory studies should be performed within 3 days prior to the first dose of TAK228 – CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO<sub>2</sub>), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, direct bilirubin, uric acid, lactate dehydrogenase (LDH), Beta-2 microglobulin, prothrombin time (PT/INR), partial thromboplastin time (PTT), hemoglobin A1c, and urine analysis, and a fasting serum glucose, triglycerides, cholesterol panel, and serum Beta-HCG in women of child-bearing potential. Fasting is defined as nothing to eat for at least 4-6 hours before blood draw.

ECHO or MUGA performed.

Quantitative immunoglobulins (IgG, IgA, and IgM) within 28 days prior to the first dose of TAK228.

HIV 1 and 2 antibody, Hepatitis C viral antibody, Hepatitis B surface antigen, Hepatitis B core antibody within 28 days prior to the first dose of TAK228.

The following staging studies should be performed within 28 days prior to the first dose of TAK228 – CT scans of neck, chest, abdomen, and pelvis; Chest X-ray – PA and lateral; and unilateral bone marrow biopsy and unilateral bone marrow aspirate. An optional PET/CT scan may be obtained within 28 days prior to the first dose of TAK228 at the discretion of the treating physician.

An electrocardiogram will be obtained within 28 days prior to the first dose of TAK228.

For correlative studies, an optional 10 ml of blood sample [2 heparin containing green top tubes (5 ml/tube)] will be collected within 3 business days prior to the first dose of TAK228. These samples will be transported within 4 hours of collection to the RPPA Core Laboratory Facility and/or Lymphoma Tissue Bank, depending on time of collection, at M. D. Anderson Cancer Center (MDACC). Blood from green top tubes will be processed for isolation of peripheral blood mononuclear cells (PBMC) using standard laboratory protocols.

For correlative studies, an optional archival tumor FFPE biopsy material collection will be occur for analysis of mutations in MTOR.

For correlative studies, an optional biopsy will be collected within 28 days prior to the first dose of TAK228 for analysis of phosphorylation in mTOR and related proteins if the patient has a tumor deemed to be safely accessible by the treating physician.

#### **EVALUATION DURING STUDY**

During the first cycle, patients will be evaluated by the treating physician in the clinic prior to the start of TAK228 (within 3 business days). A relevant history and physical examination, including performance status evaluation and vital signs, will be recorded within 3 business days of the first dose of TAK228. Patients will subsequently be assessed by the medical team on days 8, 15, and 22 (within 3 business days). At these weekly assessments, a relevant history and physical examination will be recorded. Toxicities will be graded according to the NCI CTC v4.0 during these visits.

For all cycles beyond cycle 1, patients will be evaluated by the treating physician in the clinic prior to each cycle of TAK228 (within 3 business days). A relevant history and physical examination, including performance status evaluation and vital signs, will be recorded within 3 business days of each dose of TAK228. Toxicities will be graded according to the NCI CTC v4.0 during these visits

The following laboratory studies should be performed within 3 business days prior to each cycle of TAK228 – CBC with differential, Serum chemistries - Na, K, Cl, CO<sub>2</sub>, BUN, Cr, Ca, Mg, phosphorus, total protein, albumin, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, urinalysis, uric acid, PT/PTT/INR and LDH, and a fasting serum glucose, triglycerides, cholesterol panel, and serum Beta-HCG in women of child-bearing potential.

During the first 2 cycles of therapy, patients will monitor their glucose at least once daily in a fasting state via a provided glucometer. All patients will self monitor their glucose daily in a fasting state approximately the same time each day, and if directed by the clinical trial team may require monitoring more than once per day. If no irregularities in the fasting blood glucose level are observed during a minimum of 2 consecutive months, then the frequency of in-home fasting blood glucose testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgement and approval. Fasting is defined as nothing to eat for at least 4-6 hours before blood draw.

During the first cycle of TAK228, the following laboratory studies should be performed on day 15 (within 3 business days) - CBC with differential, Serum chemistries - Na, K, Cl, CO<sub>2</sub>, BUN, Cr, Ca, Mg, phosphorus, total protein, albumin, alkaline phosphatase, AST, ALT, total bilirubin, uric acid, and LDH, and a fasting serum glucose, triglycerides, cholesterol panel. Fasting is defined as nothing to eat for at

least 4-6 hours before blood draw.

Hemoglobin A1c should be obtained prior to cycle 1 day 1, cycle 3 day 1, cycle 6 day 1, cycle 9 days 1 and cycle 12 day 1.

An electrocardiogram will be obtained pre-dose (within 28 business days) prior to start of cycle 1 and within 3 days of starting each subsequent cycle.

The following staging studies should be performed at completion of 2 cycles of TAK228 (within 5 business days prior to starting cycle 3) – CT scans of neck, chest, abdomen, and pelvis; Chest X-ray – PA and lateral; and unilateral bone marrow biopsy and unilateral aspirate if bone marrow is involved with lymphoma at baseline. An optional PET/CT scan may be obtained at completion of 2 cycles of TAK228 at the discretion of the treating physician.

The following staging studies should be performed at completion of every 2 cycles beyond the first 2 cycles of TAK228 (i.e., +/- 5 business days prior to starting cycle 5, 7, 9, and 11): CT scans of neck, chest, abdomen, and pelvis; Chest X-ray – PA and lateral; and optional unilateral bone marrow biopsy and unilateral aspirate if bone marrow is involved with lymphoma at baseline at the discretion of the treating physician; An optional PET/CT scan may be obtained at completion of every 2 cycles of TAK228 at the discretion of the treating physician, but should be considered if previously FDG avid lymph nodes remain enlarged on CT imaging or physical examination.

In consenting patients, for correlative studies, a 10 ml of blood sample [1 heparin containing green top tube and 1 purple top tube (5 ml/tube)] will be collected at each of the following time points: cycle 1 day 1 (2-4 hours after dose), and cycle 2 day 1 (2-4 hours after dose). These samples will be transported within 4 hours (+/- 2 hours) of collection to the RPPA Core Laboratory Facility and/or Lymphoma Tissue Bank, depending on time of collection, at M. D. Anderson Cancer Center (MDACC). Blood from green top tubes will be processed for isolation of peripheral blood mononuclear cells (PBMC) using standard laboratory protocols.

For correlative studies, an optional biopsy will be collected on day 14 (+/- 5 business days, within 4 hours of dosing) for analysis of phosphorylation of mTORC1/2 target proteins if the patient has a tumor deemed to be safely accessible by the treating physician and underwent Screening Biopsy.

#### **Evaluation At Completion of Study**

Patients will be evaluated by the treating physician and a relevant history and physical examination, including performance status evaluation and vital signs, will be recorded 1 week (+/- 7 business days) after completion of TAK228. Toxicities will be graded according to the NCI CTC v4.0 during this visit.

The following laboratory studies should be performed 1 week (+/- 7 business days) after completion of TAK228 – CBC with differential, Serum chemistries - Na, K, Cl, Glucose, CO<sub>2</sub>, BUN, Cr, Ca, Mg, phosphorus, total protein, albumin, alkaline phosphatase, AST, ALT, total bilirubin, PT/PTT/INR, urinalysis, uric acid, LDH, and quantitative immunoglobulins, and a fasting serum glucose, triglycerides, and cholesterol panel. In addition, an EKG should be performed 1 week (+/- 7 business days) after completion of TAK228. Fasting is defined as nothing to eat for at least 4-6 hours before blood draw.

The following staging studies should be performed 2 weeks (+/- 14 business days) after completion of TAK228 – CT scans of neck, chest, abdomen, and pelvis; Chest X-ray – PA and lateral; and optional bilateral bone marrow biopsy and unilateral aspirate if bone marrow is involved with lymphoma at baseline at the discretion of the treating physician. An optional PET/CT may be performed 2 weeks (+/- 14 working/business days) after completion of TAK228 at the discretion of the treating physician.

For correlative studies, 10 ml of blood sample [2 heparin containing green top tubes (5ml/tube)] will be collected when a patient is taken off study (+/- 14 business days). These samples will be transported within 6 hours of collection to the RPPA Core Laboratory Facility and/or Lymphoma Tissue Bank, depending on time of collection, at M. D. Anderson Cancer Center (MDACC). Blood from green top tubes will be processed for isolation of peripheral blood mononuclear cells (PBMC) using standard laboratory protocols.

Patients will be evaluated by the treating physician and a relevant history and physical examination, including performance status evaluation and vital signs, will be recorded 1 week (+/- 7 business days) after completion of TAK228. Toxicities will be graded according to the NCI CTC v4.0 during this visit.

The following laboratory studies should be performed 1 week (+/- 7 business days) after completion of TAK228 – CBC with differential, Serum chemistries - Na, K, Cl, Glucose, CO<sub>2</sub>, BUN, Cr, Ca, Mg, phosphorus, total protein, albumin, alkaline phosphatase, AST, ALT, total bilirubin, PT/PTT/INR, urinalysis, uric acid, LDH, and quantitative immunoglobulins, and a fasting serum glucose, triglycerides, and cholesterol panel. In addition, an EKG should be performed 1 week (+/- 7 business days) after completion of TAK228.

The following staging studies should be performed 2 weeks (+/- 14 business days) after completion of TAK228 – CT scans of neck, chest, abdomen, and pelvis; Chest X-ray – PA and lateral; and optional bilateral bone marrow biopsy and unilateral aspirate if bone marrow is involved with lymphoma at baseline at the discretion of the treating physician. An optional PET/CT may be performed 2 weeks (+/- 14 working/business days) after completion of TAK228 at the discretion of the treating physician.

For correlative studies, 10 ml of blood sample [2 heparin containing green top tubes (5ml/tube)] will be collected when a patient is taken off study (+/- 14 business days). These samples will be transported within 6 hours of collection to the RPPA Core Laboratory Facility and/or Lymphoma Tissue Bank, depending on time of collection, at M. D. Anderson Cancer Center (MDACC). Blood from green top tubes will be processed for isolation of peripheral blood mononuclear cells (PBMC) using standard laboratory protocols.

#### **Study Enrollment:**

The study population for this research will consist of participants from:

Only at MDACC

**Estimated Accrual:**

Total Accrual at MDACC: Phase II: Maximum 75, Minimum 45  
Estimated monthly accrual at MDACC: 3

**Screening Accrual:**

Does this study include a screening component? No

**Accrual Comments:**

This is an open label, phase II clinical trial to evaluate the safety and efficacy of TAK228 in patients with relapsed lymphoma. The maximum sample size is 75 and the minimum samples size is 24 for Phase II.

**Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)?** No

**Is this an NCI-Division of Cancer Prevention Protocol (DCP)?** No

**Statistical Considerations:**

This is an open label, phase II clinical trial to evaluate the safety and efficacy of TAK228 in patients with relapsed lymphoma. The maximum numbers of patients that will be recruited are 75 for the phase II.

The primary objective of trial is to determine the best overall response rate, defined as the combination of complete (CR) and partial (PR) response rates in patients with relapsed lymphoma when treated with TAK228. The secondary objectives are to define the safety & tolerability, overall survival, progression free survival, duration of response, determination of response associated clinical characteristics, of TAK228 in patients with relapsed lymphoma.

The overall response assessment at 2 cycles will be utilized to determine if additional accrual in each phase II cohort is warranted, but will not be the primary endpoint.

**Phase II cohort definitions and expectations**

Differences in the natural history of the lymphoma subtypes allowed on this clinical trial will require stratification. Therefore, we will separate accrued patients into three independent cohorts. As this is the first detailed evaluation of TAK228 in relapsed lymphoma, we will employ a bayesian trial design to avoid potential futility and/or toxicity.

**Cohort A**

Cohort A will be defined as aggressive lymphoma (diffuse large b cell lymphoma, follicular grade 3b, transformed lymphomas, and mantle cell lymphoma). Clinical experience with mTORC1 inhibitors in relapsed aggressive lymphoma is variable, but is most commonly reported to be 28-38% ORR.(17) It is assumed that TAK228 will have a target overall response rate at 2 cycles of 35% for this patient cohort. A response rate of 10% or lower is considered a failure and the new regimen will be rejected under this circumstance.

### **Cohort I**

Cohort I will be defined as indolent lymphoma (follicular lymphoma grade 1 – 3a, small lymphocytic lymphoma, and marginal zone lymphoma). Clinical experience with mTORC1 inhibitors in relapsed indolent lymphoma is variable, but is most commonly reported to be 11-54% ORR.(17) It is assumed that the new regimen will have a target overall response rate at 2 cycles of 45%. A response rate of 20% or lower is considered a failure and the new regimen will be rejected under this circumstance.

### **Cohort H**

Cohort H will be defined as Hodgkin lymphoma. Clinical experience with mTORC1 inhibitors in relapsed Hodgkin lymphoma is variable, but small studies have identified ORR as high as 42%, though larger studies have not yet confirmed these results.(17) It is assumed that the new regimen will have a target overall response rate at 2 cycles of 35% for this patient cohort. A response rate of 10% or lower is considered a failure and the new regimen will be rejected under this circumstance.

### **Phase II design:**

During the phase II study, patients will be treated with TAK228 at the MTD established in the sponsored trials. Three independent cohorts of patients will be enrolled: 1) patients with aggressive lymphoma (diffuse large B cell lymphoma, follicular grade 3b, transformed lymphomas, and mantle cell lymphoma); 2) patients with indolent lymphoma (follicular lymphoma grade 1 – 3a, small lymphocytic lymphoma, and marginal zone lymphoma); and 3) patients with Hodgkin lymphoma. We will run the three cohorts as three parallel trials. The maximum number of patients needed for each cohort is 25.

For each of the patient cohort, the overall response (OR) at two cycles and dose modifications required based upon toxicity (referred to below as reason for dose modification) at one cycle will be monitored. Simultaneously using Bayesian stopping boundaries calculated based on Beta-Binomial distributions. Independence was assumed between OR and Reason for dose modification.

For each of the patient cohort, the overall response (OR) at two cycles and dose modifications required based upon toxicity (referred to below as reason for dose modification) at one cycle will be monitored. Simultaneously using Bayesian stopping boundaries calculated based on Beta-Binomial distributions. Independence was assumed between OR and reason for dose modification.

For cohorts A) and H), TAK228 will be considered promising if it yields an OR rate of 35% at two cycles and a reason for dose modification rate of 30% at one cycle. A sample size of 25 in each patient cohort ensures that, if the cohort is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.297 at most, under the assumption of a 35% of OR rate. The prior probabilities of OR and reason for dose modification for the experimental regimen are modeled by beta distributions (*Beta*(0.7,1.3) and *Beta*(0.6,1.4), respectively). Denoting probabilities of OR rate and reason for dose modification rate by (pOR , pReason for dose modification) Confidential, the following decision criteria will be applied: Stop the trial if  $\text{Prob}(pOR < 35\% | \text{data}) > 0.95$  or  $\text{Prob}(p\text{Reason for dose modification} > 30\% | \text{data}) > 0.95$ .

Patients will be monitored by a cohort size of 5 after the first 15 patients according to the following stopping boundaries for OR at two cycles and reason for dose modification at one cycle. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed.

For cohorts I), TAK228 will be considered promising if it yields an OR rate of 45% at two cycles and a REASON FOR DOSE MODIFICATION rate of 25% at one cycle. A sample size of 25 ensures that, if the cohort is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.310 at most, under the assumption of a 45% of OR rate. The prior probabilities of OR and REASON FOR DOSE MODIFICATION for the experimental regimen are modeled by beta distributions ( $Beta(0.9,1.1)$  and  $Beta(0.5,1.5)$ , respectively). Denoting probabilities of OR rate and REASON FOR DOSE MODIFICATION rate by ( $p_{OR}$ ,  $p_{Reason\ for\ dose\ modification}$ ), the following decision criteria will be applied: Stop the trial if  $Prob(p_{OR} < 45\% \mid data) > 0.95$  or  $Prob(p_{Reason\ for\ dose\ modification} > 25\% \mid data) > 0.95$ .

Patients will be monitored by a cohort size of 5 after the first 15 patients according to the following stopping boundaries for OR at two cycles and REASON FOR DOSE MODIFICATION at one cycle. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Patients who are treated on study and have at least 1 disease restaging study prior to termination of study participation will not be replaced with an additional patient added to their disease cohort. Patients who are treated on study and fail to have at least 1 disease restaging study prior to termination of study participation will be replaced with an additional patient added to their disease cohort at the discretion of the principle investigator.

The duration of the study as a whole is defined first patient to start the screening period to the last patient to conclude their therapeutic period. The anticipated accrual is 3 patients per month on this trial. Thus, accrual for the study is expected to be complete in approximately two years. The total duration of the study is anticipated to be approximately three years.

#### Randomization and Stratification

There will be no randomization in this study. Patients will be stratified only based upon the lymphoma subtype into the appropriate cohort.

### Analysis Plan

For each patient cohort, summary statistics will be provided for continuous variables such as age. Frequency tables will be used to summarize categorical variables such as gender, histology, response, toxicity type and severity. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints, such as time to progression and overall survival, will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important patient characteristics will be made using the log-rank test.

### Population for Analysis

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug and had this confirmed, will not be evaluated for safety.

The patient population for efficacy analysis will include all patients who received at least one dose of study drug.

Safety and efficacy data will be reviewed after 5, 10, 15, 20, and 25 patients have completed all courses of TAK228, however, accrual will continue while this analysis is pending. If there is unacceptable study drug-related toxicity, the study will be placed on hold and no further treatment of any patient will occur until further review and discussion with the FDA. The study may proceed after appropriate amendments have been made to address the observed study drug-related toxicity.

### Efficacy Analysis

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints, such as overall survival, progression free survival, and response duration, will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression may be employed for multivariate analysis on time-to-event outcomes.

### **Safety Analysis**

Toxicity evaluation will be based on the incidence of severity and type of adverse events (including physical and laboratory). At each cycle clinic visit, patients will have vital signs (temperature, blood pressure, heart rate, and weight) measured, ECOG performance status assessed, be asked about all toxicities they have suffered, and undergo a physical exam. In addition, routine clinical laboratory testing (complete blood count, electrolytes, kidney and liver related labs) will be performed.

Does this protocol include a dose expansion component? No

### **Data Safety Monitoring Board / DSMB at MDACC:**

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:  
Not Applicable

Please explain:

This protocol is neither randomized nor blinded.

### **Protocol Monitoring:**

Does this protocol have a schedule for interim and final analysis? Yes

Provide a summary or schedule of interim analysis.

Safety and non-binding efficacy data will be reviewed after 5, 10, 15, 20, and 25 patients have completed all courses of TAK228, however, accrual will continue while this analysis is pending. If there is unacceptable study drug-related toxicity, the study will be placed on hold and no further treatment of any patient will occur until further review and discussion with the FDA. The study may proceed after appropriate amendments have been made to address the observed study drug-related toxicity. It is anticipated that a preliminary report of efficacy and safety may be presented at a national meeting such as the ASCO Annual Meeting, including the trials in progress poster session, or the American Society of Hematology Annual Meeting.

### **Protocol Monitoring Plan:**

A Bayesian dose escalation program and efficacy/toxicity monitoring to allow for cohorts which do not meet our efficacy targets to close early.

### **Intellectual Property:**

1. Does this study include any agents, devices, or radioactive compound (or No drug) manufactured at MD Anderson Cancer Center or by a contract

manufacturer?

**Investigational New Drugs (IND):**

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?

[UT MDACC](#)

IND Number: 129,368

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

**Investigational Device (IDE):**

Does this study utilize an Investigational Device? N/A

**Immunotherapy**

Is this an Immunotherapy study? No

**Moon Shots Program**

Will your protocol be funded by the Moon Shots Program? No

**Sponsorship and Support Information:**

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Takeda Pharmaceuticals, Inc.

Support Type: Industry Funding

Agent Name(s): TAK228

This Sponsor/Supporter/Granting Agency will receive data.

**Regulatory Requirements**

**Radioactive Material:**

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Does this study involve the administration of radioisotopes or a radioisotope labeled agent? N/A

[Click here for help](#)

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**Biosafety:**

Does this study involve the use of Recombinant DNA Technology such as No

DNA nucleotide, RNA nucleotide, genetically modified human cells, animal cells, bacteria, or virus?

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve human/animal tissue other than blood derived hematopoietic stem cells? N/A

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

**Laboratory Tests:**

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

Yes

No

Not Applicable For This Protocol

**Manufacturing:**

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No

**Student/Trainee Information:**

Is this research being conducted as a partial fulfillment for completion of a degree? No