PROTOCOL NO. RP6530-1401

A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma

PROTOCOL NUMBER: RP6530-1401

TRIAL DRUG: RP6530

IND NUMBER 124584

SPONSOR:

PRINCIPAL INVESTIGATOR

SPONSOR'S MEDICAL EXPERT

VERSION : Version 7.0, Dated 23 May 2018

Clinical Trial Protocol Statement of Compliance

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **<Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the PI/Co-PI/Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Sposnor's Medical Expert, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted sponsor responsibilities to the CRO and the Study PI/Co-PI as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

Amendment history

A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma

Amendment# /date	Reference to section	Summary	Rationale
Amendment 1/27 Jan 2014	**-Section 4.1: Inclusion criteria # 2 & synopsis**	**Inclusion criteria # 2 is updated to:** Disease status defined as: • Refractory to or relapsed after ≥ 1 prior treatment lines. • Patients are not eligible for transplantation or any standard therapy and / or approved known to be life prolonging or life saving (patients who are eligible for transplantation or any standard and /or approved therapy known to be life prolonging or life-saving and have declined transplantation or any standard and /or approved therapy known to be life prolonging or life saving are eligible for the study)	In order to accommodate the use of approved therapies prior to enrollment of patients on the study, the inclusion criterion is updated as per the directive of regulatory authority. -
Amendment 1/31 Jan 2015	**Section 6.2: Adverse event/SAE causality assessment & synopsis**	The causality assessment is updated as follows: For this study, the causality will be assessed as related and not related. **Related:** All toxicities should be considered to be related to RP6530 unless there is a clear alternative explanation. **Not related:** If there is no temporal association, or another etiology has been identified as the cause, or the trial treatment cannot be implicated based upon the current information.	As a part of causality assessment, the updated criterion will be used to determine the relationship of adverse event with study drug as per the directive of regulatory authority.
Amendment 1/31 Jan 2015	**Section 6.6: Dose Limiting toxicity & synopsis**	The following sentence is added for safety assessment. **All toxicities should be considered to be related to RP6530 unless there is a clear alternative explanation.** A toxicity will be considered dose-limiting if it occurs during the first Cycle (4-weeks) treatment with RP6530 and is considered related to RP6530.	As a part of causality assessment, the updated criterion will be used to determine the relationship of adverse event with study drug as per the directive of regulatory authority.

Amendment#/date	Reference to section	Summary	Rationale
Amendment 2/21 May 2015	**Section 3.3.1: Dose Escalation procedure**	The dose escalation criteria and optimal dose are clarified. If two of the first 3 patients in a cohort experience a DLT, that dose level will be defined as exceeding MTD, no further dose escalation will occur. The previous dose level will be considered the MTD and will be expanded to further elucidate safety, to define PK, and to evaluate efficacy. An optimal dose is defined as the threshold dose at which the study drug is clinically active / efficacious (shows complete response or partial response) in a specific disease population and is at or below the maximum tolerated dose.	The dose escalation criteria and optimal dose are clarified as requested by the Clinical Research Committee (CRC) of MDACC.
	Section 3.6.1 Dosage form and strengths of IMP	The strengths of tablet is corrected to 200 mg and 400 mg.	Correction of typo error.
	Section 3.8 Study stopping rule	Frequency of safety monitoring by DRG in expansion cohort is clarified. The DRG will continue to monitor toxicity for serious adverse events as well as for toxicity trends that may be of concern at interval of 3 months from initiation of expansion cohort to completion of the study. Toxicity will be monitored across cohorts combined together, as the expansion will be done at the specific dose (either MTD or optimal dose).	Frequency of monitoring safety in expansion cohort is clarified as requested by the Clinical Research Committee (CRC) of MDACC.
	Section D: Schedule of assessment	The table of "schedule of assessment" is simplified and typo errors are corrected to match the text with study protocol	-
Amendment 3/ 20 January 2016	**Synopsis**	Dose Level -1 is corrected to 100 mg BID	Correction of typo error.
	Contact information	Clinical laboratory information has been updated	Protocol clarification
	Section 4.1 Inclusion criteria	**Inclusion criteria # 9 is corrected.** Female patients of child-bearing potential, and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530. A barrier method of contraception must be included.	Correction of typo error
	Section 8.2 Screening	The following sentence is updated. Patient registration will be done as per **site's practice**. **Sites** will assign a patient identification number and dose level.	Protocol clarification as study is expanded to other sites.

Amendment#/date	Reference to section	Summary	Rationale
	Section 8.3 Laboratory investigations	The sentence updated is updated to add local laboratory facilities. The investigations will be performed at MDACC laboratory/local laboratory or central laboratory as decided by sponsor.	Sentence is updated to extend the study to the other sites
	Section 8.10 Correlative/ Exploratory biomarkers	The title is updated.	Typo correction.
	Section 9.2 Sample size determination and synopsis	The sentence is updated as This trial will enroll up to 58 patients at **5-10 sites**	New sites will be added to expedite recruitment
Amendment 4/ 25 April 2016	**Section 3.3.1 Dose escalation procedure**	The additional cohort ***RP6530 800 mg with food (Cohort 3a)*** is added to dose escalation cohorts. Patients of ***subsequent cohorts (cohort 4 and 5) to receive the study drug after food.***	Dosing recommendations are in line with the findings of food effect study that suggests increased bio-availability of the study drug if administered after food as compared to fasting state.
	Section 3.3.2 Intra dose escalation	The following sentence is added in intra dose escalation At the discretion of treating investigator, dose escalation may be done in patient who received lower doses (de-escalation) due to safety reason.	Protocol clarification
	Section 3.6.3 Preparation and administration of investigational product	Dosing recommendations are added for drug administration after food. In case of fasting cohorts, patients should swallow RP6530 tablets whole with a full glass (approximately 8 ounces) of water in a fasting state. ***In fed cohorts, RP6530 tablets will be self-administered orally twice daily after food (30 minutes after breakfast and dinner).***	Dosing recommendations are updated.
	Section 4.1 Inclusion criteria and synopsis	**Inclusion criteria #2** Disease status defined as: • Refractory to or relapsed after ≥ 1 prior treatment lines. • Patients are not eligible for transplantation or any standard therapy and / or approved therapy known to be life prolonging or life saving (patients who are eligible for transplantation or any standard and /or approved therapy known to be life prolonging or life saving and have declined transplantation or any standard and /or approved therapy known to be life prolonging or life saving are eligible for the study) **is updated to** Disease status defined as:	Protocol clarification

Amendment#/date	Reference to section	Summary	Rationale
		• Refractory to or relapsed after ≥ 1 prior **standard therapy and/or FDA approved therapy.**	
	Section 5.2 Concomitant medication	The initiation or escalation of growth factor therapy is modified as Patients who have been on stable erythropoietin or darbepoetin therapy for **two weeks** preceding trial treatment may remain on the same dose during the first month. Growth factor therapy, if initiated in the first month for the treatment of study drug **related** AE (e.g. RP6530 related neutropenia), such patients will be discontinued.	Protocol clarification
	Section 6.1: Adverse events	Adverse events section is updated. **All Grade 3 and grade 4 AE s irrespective of causality constitute clinically significant AE.**	Protocol clarification
	Section 6.4.: Recording of AE's and SAE	The reporting of persistent and recurrent AE's is updated as follows If a persistent AE becomes more severe or lessens in severity, it should be recorded **at once with highest grade of severity** on a SAE Report Form and/or AE CRF.	Protocol clarification
	Section 6.6.1 Determination of dose limiting toxicity	Minimum safety requirement for DLT is updated as follow. Minimum safety requirements will be met if, **during Cycle 1 of treatment,** • The patient receives at least 80% of planned doses of RP6530 doses **OR** ***received RP6530 for the first 21 days continuously;*** • Completes all required safety evaluations ***(at least for three visits after the first dose)***; • And is observed for at least 28 days following the first dose of RP6530 in case of ***related*** adverse event.	Protocol clarification
	Section 6.7 Dose modifications	The following sentences is updated in the dose modification section. If serum creatinine >3 x baseline or >3 x ULN, hold dose until ≤ grade 1. Monitor serum creatinine at least twice a week until resolution to ≤ grade 2, and then at least one week until it resolves to ≤ grade 1 The following note is added Note: In the event of ***unrelated*** haematological/non-haematological toxicity (e.g. toxicity due to underlying disease condition or co-morbidity), the dose modification or dose delay will be done at the discretion of PI/CO-PI after evaluating the safety of the patient and need for dose modification	Protocol clarification

Amendment#/date	Reference to section	Summary	Rationale
	Section 8.6 **Skin biopsy & Appendix D**	The following statement is updated to clarify the evaluation of TCR gene rearrangement in disease assessment. Clonality of TCR gene rearrangement will be evaluated ***as part of standard of care and will be an optional***	Protocol clarification
	Section 8.9 **Pharmacodynamics & Appendix D**	The statement is updated as PD samples (pAKT) will be performed on C1D1 (pre-dose and 1 hr later), C1D8 (pre-dose) and C1D22 (pre-dose); C2D1 (pre-dose) and C3D1 (pre-dose) and/ at EOT in five Sezary syndrome patients.	Protocol clarification
	Section 8.10 **Correlative/ Exploratory biomarkers/ assessment & Appendix D**	The sentence is updated as Correlative biomarkers (e.g. sIL2R CTACK (PTCL); CD30 (MF), IL-31 and IL-32 (CTCL)) will be performed at screening, C3D1 (pre-dose and 1 hr later); at EOT and/ or to confirm a response. Blood will be collected for these biomarkers, serum aliquots will be prepared and shall be stored at below -70^{0}C until analysis. The decision to analyse the serum samples will be taken at later stage only if required or deemed necessary by the investigator/sponsor.	Protocol clarification.
	Section 9.2 Sample size determination and synopsis	The sentence is updated as The actual number of dose cohorts will depend upon the MTD/optimal dose (or recommended dose).	Protocol clarification
	-	Correction of typo errors.	-
Amendment 4/ 20 June 2016	**Section Contact Information**	The change of PI at MDACC. Dr. Mandeleine Duvic to Dr. Auris Huen	Adminsitrative Change
	Appendix D	Chemistry Panel I includes Total bilirubin, ALP, AST, ALT, GGT, LDH and Serum electrolytes (Sodium, Potassium, Bicarbonate, Chloride, Magnesium, Phosphorus and Calcium).	Protocol clarification.
	Appendix D	Lymph node biopsy or aspirate: The lymph node will be required to perform only if the diagnosis is not confirmed at the baseline; and if required at other time points.	Protocol clarification
Amendment 5/ 18 April 2017	**Section 4.1: Inclusion criteria # 2 & synopsis**	**Inclusion criteria # 2 is updated to:** Disease status defined as: • Refractory to or relapsed after ≥ 1 prior treatment lines.	The inclusion criterion is updated as per the directive of regulatory authority.

Amendment#/date	Reference to section	Summary	Rationale
		• Patients who are not eligible for transplantation or any standard and / or approved therapy known to be life prolonging or life saving (patients who may be eligible for transplantation or any standard and /or approved therapy but have declined therapy, or in the investigators opinion based on the patient's condition, an investigational therapy may benefit more than existing approved therapies are eligible for the study).	
	Section: Contact information	Change of Medical monitor. Neil Sankar, MD will be the medical monitor of the study.	Administrative change
	Section 3.2 and 3.3: Trial Design	Dose Escalation schedule is updated and the dose of Dose Expansion is defined.	RP6530 800 mg BID (Fasting) is considered as a MTD dose in patients with T-cell lymphoma. Therefore, this dose will be used for Dose Expansion.
	Section 6.3 **RP6530 Dose Modifications for Non-Hematologic Toxicities**	Algorithm (Appendix M) for monitoring liver enzymes has been added.	Grade III elevation of ALT and/or AST have been observed with RP6530 treatment in Dose Escalation. Most transaminase elevations were reversible with dose interruption. Multiple lines of evidence from literature suggest that this hepatotoxicity was immune mediated. In in view of this, frequent monitoring of liver enzymes is recommended in patient presenting with transaminitis. Steroid can be initiated by the investigator after clinical evaluation of patient.
	Section 8: Trial assessment and treatment and Appendix D	The procedures to be performed in Dose Expansion is defined.	Protocol clarification

Amendment#/date	Reference to section	Summary	Rationale
Amendment 6, Dated 23 May 2018	**Section 8:** Design of trial	The criteria for study closure is defined as follow: The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued treatment due to any reason, whichever is earlier. At the end of the study, all ongoing patients will be given the opportunity to enroll in an open-label compassionate use study protocol.	Protocol clarification
	Section 8: Trial assessment and treatment and Appendix D	The post Cycle 8 procedures related to safety, efficacy and drug administration has been clarified. Clarification for laboratory investigations added.	Protocol clarification
		Administrative changes or safety updates added.	Administrative change

Clinical Trial Protocol Approval Page

A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma

PROTOCOL NUMBER:	RP6530-1401
TRIAL DRUG:	RP6530
IND NUMBER:	124584

Sponsor's Medical Expert	**Signature**	**Date**
Sponsor's Representative	**Signature**	**Date**
Bio-statistician	**Signature**	**Date**

RP6530-1401

Protocol Acceptance Form

A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma

PROTOCOL NUMBER:	RP6530-1401
TRIAL DRUG:	RP6530
IND NUMBER:	124584
FINAL:	Version 7, Dated 23 May 2018

Principal Investigator	**Signature**	**Dated**

PROTOCOL SYNOPSIS

Title of Trial:	A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma
IND Number	124584
Protocol Number:	RP6530-1401
Sponsor:	Rhizen Pharmaceuticals SA
Study Duration	Approximately 10 months to accrue, plus follow-up
Trial Population and Trial Centers:	This study will be conducted in relapse/refractory T-cell lymphoma patients at 5-10 US sites.
Rationale:	Phosphoinositide-3-kinases (PI3Ks) are pivotal in various cellular functions including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta (δ) and gamma (γ) isoforms of PI3K are highly expressed in cells of hematopoietic origin, and often dysregulated in various hematologic malignancies. Because these isoforms contribute to the development, maintenance, transformation, and proliferation of immune cells, dual targeting of PI3K δ and γ represents a promising approach in the treatment of various lymphomas. RP6530 is a novel, highly specific dual PI3K δ/γ inhibitor with nanomolar inhibitory potency at the enzyme and cellular level. Besides, RP6530 is effective in inhibiting Akt phosphorylation and inducing apoptosis in various lymphoma and leukemic cell lines and patient derived primary CTCL cells.
Study objectives	**Primary Objective** • To evaluate the safety and the maximum tolerated dose (MTD) of RP6530 in patients with relapsed/refractory T-cell lymphoma (PTCL/CTCL). • To evaluate the pharmacokinetics (PK) of RP6530. **Secondary Objectives** • To examine the pharmacodynamic (PD) effects of RP6530. • To assess the overall response rate (ORR) and duration of response (DoR) in patients with relapsed/refractory T-cell lymphoma. **Exploratory Objectives** • Correlation of treatment outcomes with biomarkers which include but are not limited to quantitative and qualitative measurements of cytokines, chemokines and aberrations indicative of PI3K function and RP6530 efficacy.
Study End Points	**Primary Endpoint** • AE, SAE, clinically significant AE and dose limiting toxicities (DLT). • PK parameters (including $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, λ_z, and $t_{½}$) of RP6530 **Secondary end points** • Inhibition of pAKT by RP6530. • ORR as defined as sum of CR and PR rates; and DoR. **Exploratory end points** • Correlative biomarkers (e.g. serum cytokines and chemokines).
Study Design	This is a two part Phase 1/1b study. The first part is a Phase 1 dose escalation, 3+3 design, open-label, MTD determination study of RP6530 in patients with relapsed/refractory T-cell lymphoma (PTCL/CTCL). The second part is Phase 1b, dose expansion, open label study to be conducted once the MTD/optimal dose has been confirmed in dose escalation phase. 20 patients of each indication will be enrolled (20 for PTCL and 20 for CTCL). Tablet RP6530 will be administered orally

twice a day in 28-days cycle in absence of disease progression, unacceptable toxicity, or withdrawal from treatment.

Phase I Dose Escalation:
Sequential dose escalation will begin with Cohort 1. A minimum of three patients of either CTCL or PTCL will be entered into each opened dose level (cohort). The first cohort of patients will receive RP6530 at 200 mg twice a day (BID). Dose levels will be increased in successive increments according to the dose escalation scheme in the Table below. Dose escalation will continue until the MTD/optiomal dose has been identified or as determined by the DRG based on the available safety, PK and/or efficacy data. Dose determination will be documented appropriately.

Dose Escalation Schedule

Dose Level	Dose (RP6530)	Dosing recommendation	Patients (n)
1*	200 mg BID	Fasting	3-6
2	400 mg BID	Fasting	3-6
3	800 mg BID	Fasting	3-6
3a	800 mg BID	After food	3-6

*If not tolerated or DLT occurs in over 33% of patients treated, a dose level of -1 (i.e. 100 mg BID) will be tested.
** In fasting cohorts, patients will fast 2 hours prior to study drug administration and 1 hour after administration. In Fed cohort (After food), patients to take study after food (30 minutes after breakfast and dinner).

Note:
- The actual number of dose cohorts explored will depend upon the MTD and the safety profile observed during the conduct of the trial. Intermediate dose levels and alternative dosing schedules may be explored if deemed appropriate.
- Intra-subject dose escalation will be performed once the higher dose is considered safe and tolerable.

Phase Ib, dose expansion:
Once the MTD/optimal dose has been confirmed, patients who complete the Dose Escalation Phase will be permitted to enter the expansion cohorts (Phase Ib). Additional CTCL and PTCL patients may be enrolled to reach a maximum of 58 patients (including the Phase I patients) in each of the CTCL and PTCL groups.

The DRG may recommend to the Sponsor early termination of a study group if none of the first 10 patients achieve an objective response (PR or >), or </= 6 of the first 20 patients achieve an objective response (PR or >), by the second efficacy assessment which is estimated on Cycle 8/Day 1 (C8D1).

Dose Expansion Schedule

Dose Level	Dose (RP6530)	Patients (n)
CTCL	RP6530 800 mg Fasting	20
PTCL	RP6530 800 mg Fasting	20

Number of Patients:	The study will enroll approximately 58 patients; up to 18 during the dose escalation phase and 40 patients in the expansion phase. **Note:** The total number of patienst in phase I may exceed depending on MTD.
Trial Drug(s), Dose, and Mode of Administration:	**RP6530:** Dosing will begin on Cycle 1/Day 1 (C1D1) with continuous oral twice daily dosing (BID) in 28 days cycle. The dose and schedule of RP6530 will be determined during the dose escalation phase of the study, depending on PK and safety assessments. RP6530 will be self-administered by the patients. Tablet (s) of relevant strength should be taken at approximately the same time each day. In case of fasting state, patients will fast 2 hours prior to study drug administration and 1 hour after administration. In case of Fed state (After food), patients to take study after food (30 minutes after breakfast and dinner). The expected duration of subject participation in the study will be 8 months. Treatment will be continued in patients experiencing clinical benefit for 2 years unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI-Co-PI after consultation with Sponsor on case to case basis. The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up.
Baseline Lab Evaluation (Local Lab)	• CBC with differential • Serum chemistry • Serology to rule out active Hepatitis B, C or HIV infection • Serum pregnancy test
Instrumental Tests	• Computed tomography (CT) (MRI/PET scan as required) at screening. disease will be assessed on C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the disctetion of PI/Co-PI. • Bone marrow biopsy at screening and EOT and as indicated by study protocol. • Skin biopsy at screening, on C3D1 (± 7 days) and/or to confirm a complete response.
Assessment of Response	PTCL patients will be evaluated according to the International Working Group Revised Response Criteria for Malignant Lymphoma (IWG) Cheson et al. 2007). Bone marrow disease alone may be used to assess response, as determined by the morphology of repeat bone marrow biopsy. Assessment of CTCL response and progression will be evaluated according to the Response Criteria in Mycosis Fungoides and Se´zary Syndrome by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) ISCL/EORTC crietria. For skin scoring, the modified Severity Weighted Assessment Tool (mSWAT) will be used. For local index lesion skin scoring, the Composite Assessment of Index Lesion Severity will be used. Additional disease specific crieteria will be used if deemed necessary.

Dose-Limiting Toxicity	Toxicity will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE).
	All toxicities should be considered to be related to RP6530 unless there is a clear alternative explanation. A toxicity will be considered dose-limiting if it occurs during the first cycle (4 weeks) of treatment with RP6530 and is considered possibly related to RP6530. Dose-limiting toxicities will be defined as the following:
	• Hematological DLTs:
	  • Grade 4 Anaemia
	  • Grade 4 neutropenia (absolute neutrophil count [ANC] <500/µL) for >7 days, or Grade ≥3 febrile neutropenia (ANC <1000/µL with fever >38.5ºC [101ºF]
	  • Grade 4 thrombocytopenia for >7 days, or grade ≥3 thrombocytopenia associated with bleeding
	• Non-Hematological DLTs:
	  • Grade ≥3 non-hematologic toxicity with exception of:
	  o Grade ≥3 diarrhea or nausea that does not resolve to ≤ Grade 2 within 48 hours despite treatment; and
	  o If ≥1.5 ULN of bilirubin or >3 ALT/AST elevation that does not resolve to ≤ Grade 1 within 7 days
	• Treatment delay of ≥14 days due to unresolved toxicity
	• Non-hematologic toxicity of Grade 2 (at any time during treatment) that in the judgment of the DRG, is dose-limiting.
	• For certain toxicities such as laboratory assessments without a clear clinical correlate (e.g. lipase increase without signs of a clinical pancreatitis) a discussion between the Investigator and Medical Monitor may take place if this adverse event (AE) should be assessed as DLT necessitating dose reduction.

Inclusion Criteria:	1. Histologically confirmed T cell Non-Hodgkin Lymphoma (T-NHL) as approved by the Medical Monitor or PI/Co-PI.
	2. Disease status defined as:
	  • Refractory to or relapsed after ≥ 1 prior treatment lines.
	  • Patients who are not eligible for transplantation or any standard and / or approved therapy known to be life prolonging or life saving (patients who may be eligible for transplantation or any standard and /or approved therapy but have declined therapy, or in the investigators opinion based on the patient's condition, an investigational therapy may benefit more than existing approved therapies are eligible for the study).
	3. Patients with a measurable or evaluable disease.
	  • In case of radiologically measurable lesions, the longest diameter should be ≥ 2 cm in PTCL patients.
	  • PTCL patients with non-measurable lesions but assessable disease (e.g. marrow disease without other radiographically measurable disease) can be enrolled in dose-escalation phase as approved by PI/Co-PI.

	4. Adequate organ system function, defined as follows: • Patients with haemoglobin levels and/or neutrophil and platelet counts under these values will be eligible in case abnormalities are due to tumor dissemination or infiltration and according to physician's discretion and under his direct responsibility a. Hemoglobin ≥8 g/dL b. Absolute neutrophil count (ANC) ≥0.75 x 10^9/L c. Platelets ≥50 x 10^9/L • Total bilirubin ≤1.5 times the upper limit of normal (ULN) • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN without liver involvement or 5 x the ULN if there is known liver involvement. • Creatinine ≤ 2.0 mg/dL OR calculated creatinine clearance ≥50 mL/min as calculated by the Cockcroft-Gault method 5. ECOG performance status ≤2. 6. Life expectancy of at least 12 weeks. 7. Patients must be ≥18 years of age. 8. Ability to swallow and retain oral medication. 9. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential, and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530. A barrier method of contraception must be included. 10. Male patients willing to use adequate contraceptive measures throughout the study period and for 12 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530. 11. Willingness and ability to comply with trial and follow-up procedures. 12. Ability to understand the nature of this trial and give written informed consent.
Exclusion Criteria:	1. Any cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) in the last 3 weeks or the last 5T1/2 of the agent, whichever is shorter. Limited palliative radiation <2 weeks. 2. Autologous hematologic stem cell transplant within 3 months of study entry. Allogeneic hematologic stem cell transplant within 12 months. Active graft-versus-host disease. 3. Active HBV, HCV or HIV infection. 4. Use of an investigational drug in the last 4 weeks prior to the first dose of RP6530. 5. Therapy with GS-1101 (CAL-101, idelalisib), IPI-145, TGR-1202 or any drug that specifically inhibits PI3K/ mTOR (including temsirolimus, everolimus), AKT or BTK Inhibitor (including Ibrutinib) in last 6 months. 6. Patient has received wide field radiotherapy (including therapeutic radioisotopes such Yttrium-90) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to starting RP6530 or has not recovered from side effects of such therapy.

	7. Ongoing immunosuppressive therapy including systemic corticosteroids (prednisone or equivalent ≤10 mg daily allowed as clinically warranted). Patients are allowed to use topical or inhaled corticosteroids. 8. Known history of drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension. 9. Patients with uncontrolled Diabetes Type I or Type II (HbA1c >8% assessed locally). 10. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: • Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV) • QTcF > 470 msec • Angina not well-controlled by medication • Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months • Active or uncontrolled severe infections requiring IV antibiotics • Patients with hemophilia or Von Willebrand's disease should be excluded. 11. Herbal preparations/medications must be discontinued 7 days prior to first dose of study drug. 12. Presence of other active cancers, or history of treatment for invasive cancer ≤3 years. Patients with stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e. non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 13. Women who are pregnant or lactating. 14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 15. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol. 16. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.
Statistical Methodology:	This is an open-label, dose-escalation study to determine the MTD (or recommended dose based on available safety, PK and response data) to support of dose determination for further clinical studies, and preliminary information on the safety profile; and to evaluate PK profile and anti-tumor activity of RP6530 given as a single agent in patients with T-cell lymphoma. This trial will enroll approximately 58 patients. The actual number of dose escalations will depend upon the MTD/optimal dose (or recommended dose).
Biomarker Assessments:	During the treatment blood samples will be taken for exploratory evaluation of relevant biomarkers. The analyses for biomarkers are exploratory, and will not be used to guide treatment decisions. The results may be pooled with data from other studies to generate hypotheses to be tested in future studies.

CONTACT INFORMATION	
SPONSOR:	**Rhizen Pharmaceuticals SA** Fritz-Courvoisier 40, Ch-2300 La Chaux-de-Fonds, Switzerland. Tel +41 32 580 0113 Fax +41 32 580 0175
PRINCIPAL INVESTIGATOR STUDY SITE	**Auris Huen, MD** Assistant Professor of Medicine and Dermatology, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX TEL: 1 713- 745-113 FAX: 1 713- 745-3597 EMAIL: aohuen@mdanderson.org
SPONSOR REPRESENTATIVE	**Ajit Nair, PhD** Rhizen Pharmaceuticals SA Fritz-Courvoisier 40, Ch-2300 La Chaux-de-Fonds, Switzerland. Tel +41 32 580 0113 Fax +41 32 580 0175 EMAIL: an@rhizen.com
SPONSOR'S MEDICAL EXPERT	**Prajak Barde, MD** Rhizen Pharmaceuticals SA Fritz-Courvoisier 40, Ch-2300 La Chaux-de-Fonds, Switzerland. Tel: +1 (301) 250-5591 Fax +41 32 580 0175 EMAIL: pjb@rhizen.com
STATISTICIAN	**Michael Chen, PhD** Consultant Statistician, Tel: +01 908 500 9334 Fax: +41 32 967 9596
CENTRAL CLINICAL LABORATORY FOR PK	**NorthEast Bioanalytical Laboratories** 925 Sherman Avenue, Hamden, CT 06514, USA

List of Abbreviations

ADME	absorption, distribution, metabolism, excretion
AE	adverse events
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT (SGOT)	Alanine aminotransferase
ANC	absolute neutrophil count
AST (SGPT)	Aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{0-t}	area under the plasma-concentration time curve from zero up to the last measureable concentration
AUC_{last}	area under the concentration time curve at last dose
BID	twice daily
B-NHL	B-non-hodgkins lymphoma
BSA	bovine serum albumin
BTK	bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CLL	chronic lymphocytic leukemia
C_{max}	peak drug concentration
CRF	case report form
CSF	colony-stimulating factor
CTCL	cutaneous T-Cell Lymphoma
CTCAE	Common Terminology Criteria for Adverse Events
CT	computerized tomography
CVA	cerebro vascular accident
DRG	Data Review Group
DHEA	Dehydroepiandrosterone
DLT	dose limiting toxicity
DoR	duration of response
EC50	the dose of a drug that is pharmacologically effective for a 50% response in a biological system
ECG	Electrocardiogram
ECHO	Echocardiography (EK-o-kar-de-OG-rah-fee)
ECOG PS	eastern cooperative oncology group performance status
EORTC	European Organisation For Research and Treatment of Cancer
FACS	fluorescence activated cell sorter
FSH	follicular stimulating harmone
GCP	good clinical practices
GGT	gamma glutamyl transpeptidase
HBV	hepatitis B virus
HbA1c	glycated hemoglobin
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immune deficiency virus
HNSTD	Highest Non-Severely Toxic Dose
HTRF	homogeneous time resolved fluorescence
IB	investigator brochure

ICH	International Conference on Harmonization
IEC	Independent ethics committee
IMP	investigational medicinal product
ISF	investigator site file
ISCL	International Society For Cutaneous Lymphomas
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	Lower Limit of Normal
MTD	maxmum tolerated dose
MDACC	MD Anderson Cancer Center
MRI	Magnetic Resonance Imaging
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MF	Mycosis Fungoides
NCI	national cancer institute
nM	nano molar
NOAEL	no-observed-adverse effect level
NYHA	new 20hos heart association
ORR	20hospho response rate
pAKT	20hosphor AKT
PD	Pharmacodynamics
PET	positron emission tomography
PDGF	platelet derived growth factor
PFS	progression-free survival
PI	principle investigator
PI3K	phosphoinositide-3-kinase
Pis	20hosphor inositid lipids
PK	Pharmacokinetics
PP	per protocol
PR	partial response
PT/INR	prothrombin Time/international Normalized Ratio
PTCL	Peripheral T cell Lymphoma
QA	quality assurance
QTcF	fridericia's (QTcF) formulas
SAE	serious adverse events
SAP	statistical analysis plan
SAS	statistical analysis software
SDV	source document verification
SD	Stable disease
SS	Sezary Syndrome
STD10	severely toxic dose in 10% of animals
SOP	standard operating procedures
mSWAT	Modified Severity Weighted Assessment Tool
TIA	transient ischemic attack
TLS	tumor lysis syndrome
TKI	tyrosine kinase inhibitor
T-NHL	T-non-hodgkins lymphoma
TSH	thyroid stimulating harmone
ULN	upper limit of normal

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1. INTRODUCTION

1.1 Background

Phosphoinositide-3 kinase (PI3K) belongs to a class of intracellular lipid kinases that phosphorylate the 3 position hydroxyl group of the inositol ring of phosphoinositide lipids (PIs) generating lipid second messengers. While α and β isoforms are ubiquitous in their distribution, expression of δ and γ is restricted to circulating hematogenous cells and endothelial cells.

The scientific evidence for PI3K involvement, in particular the δ and γ isoforms in various cellular processes stems from studies using small molecule inhibitors and gene-targeting approaches. Although PI3Kδ expression has been assigned to B-cells and PI3Kγ is associated with T-lymphocytes and neutrophils, there appears to be a significant synergy rather than a redundancy between the two isoforms in various leukemias and lymphomas. In addition dual inhibition is expected to result in better targeted destruction of abnormal lymphocytes. In relapsed/refractory T-cell lymphomas for instance, blockade of the PI3K δ/γ isoforms at clinically achievable concentrations could potentially prevent T-cell activation/proliferation and alteration of tumor microenvironment with the former attributed to the γ and the latter to the δ isoform. Simultaneous inhibition of PI3K δ/γ isoforms was shown to prolong survival in a mouse model of T-cell acute lymphoblastic leukemia. Dual targeting of PI3K δ/γ therefore is strongly implicated as an intervention strategy in leukemias/lymphomas that are hard to treat by conventional means due to the added anti-inflammatory potential that helps modulate the tumor microenvironment.

Many PI3K inhibitors are in clinical development including PI3K δ specific inhibitor Idelalisib (by Gilead; now approved by USFDA for CLL and FL)[1-6] and PI3K δ and γ inhibitor IPI-145 (by Infinity Pharmaceuticals)[7]. While Idelalisib and IPI-145 have reported ALT/AST elevation and neutropenia as major side effects, IPI-145 has additionally reported opportunistic infections. RP6530 has greater safety margin, with several fold selectivity over α and β isoforms with equipotency against PI3K δ and γ isoforms. Based on the 28-day tolerability studies in rat and dog, monitoring of liver and thyroid parameters is advised since these were the major target organs noted during repeat dose toxicity studies in rats and dogs.

1.2 RP6530

RP6530 is a highly specific and orally available dual PI3K δ/γ inhibitor with nanomolar inhibitory potency and several fold selectivity over the α and β PI3K isoforms. Chemically, RP6530 is an isoflavone substituted adenine.

The specificity of RP6530 towards PI3K δ and γ is evidenced by >1000 and >100 fold selectivity over α and β isoforms in an enzyme based assay. PI3K δ and γ isoforms are expressed in hematopoietic cells and contribute to their development, maintenance, transformation and proliferation. Although PI3K δ expression has been assigned to B-cells while PI3K γ is associated with T-lymphocytes and neutrophils, there appears to be a significant synergy rather than a redundancy between the two isoforms in various leukemia's and lymphomas. Dual targeting of PI3K δ/γ therefore is strongly implicated as an intervention strategy in leukemia/lymphomas that are hard to treat by conventional means.

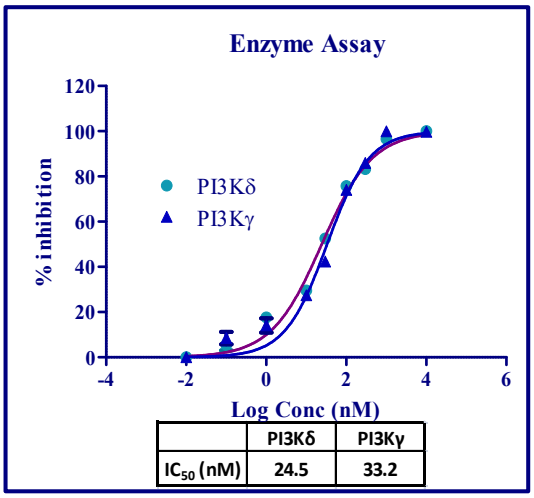
1.3 Summary of RP6530 Preclinical Evaluations

1.3.1 In Vitro Activity

Potency of RP6530 against human PI3K δ and γ was evaluated in a HTRF based enzyme assay in the presence of 100 µM ATP. Selectivity over the other two isoforms, namely, α, and β were also determined[8-11]. Data demonstrated the specificity of RP6530 towards PI3K δ and γ with >10000 and >100-fold selectivity over α and β isoforms, indicating that the primary mode of action of this compound is via dual inhibition of the δ and γ isoforms (Figure 1). Functional selectivity of RP6530 in a 245 Kinase Panel[12] indicated >50 fold selectivity over other tyrosine and serine/threonine kinases.

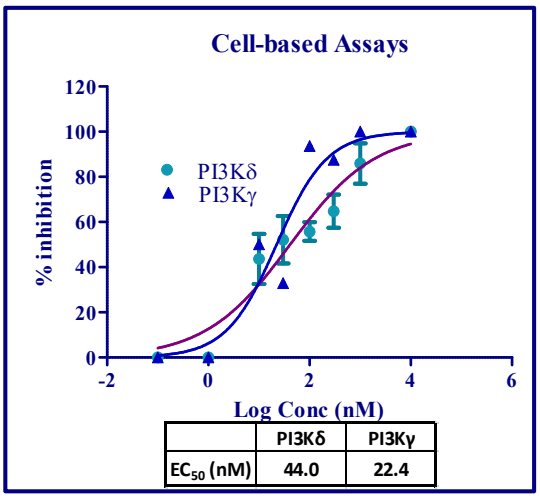
Cellular specificity towards PI3Kδ and γ was determined in an anti-IgM induced human B cell proliferation[13] and complement component 5a (c5a) induced pAKT in RAW macrophages[14] wherein potency of RP6530 was equivalent to the enzyme assay. PI3K α or β-mediated phosphorylation of AKT by platelet-derived growth factor (PDGF)[15] or lysophosphotidic acid[16] in 3T3 fibroblasts mediated through α or β, isoforms of PI3K was determined by Western blotting. Results were in line with enzyme inhibition data with the fold-selectivity being maintained for α and β (Figure 2).

Figure 1: PI3K isoform enzyme assays



	PI3Kδ	PI3Kγ
IC_{50} (nM)	24.5	33.2

Figure 2: PI3K isoform cell-based assays



	PI3Kδ	PI3Kγ
EC_{50} (nM)	44.0	22.4

Proliferation of immortalized T and B-leukemic cells representative of various indications was determined by a MTT assay[17] (Table 1). Cells were incubated with RP6530 for different time-periods (72 -96 h) based on their doubling time. Data demonstrated the ability of RP6530 to inhibit leukemic cell proliferation albeit with different potencies based on the cell type.

Overall, a 50% growth inhibition for majority of B, T, and monocytic cell lines was achieved at a concentration between 0.5 -7.5 µM of RP6530.

Subsequent to cell viability, the effect of RP6530 on AKT phosphorylation[18-22] and induction of apoptosis was determined[23-27] (Figure 3). AKT, a serine threonine kinase mediates the downstream effects of PI3K activity and modulates several cell processes including survival and growth.

Reduction of pAKT by RP6530 in representative cell lines was determined by Western blotting using a phospho-AKT (Ser473) antibody.

Figure 3. Reduction of pAKT by RP6530 in cell lines by Western blotting

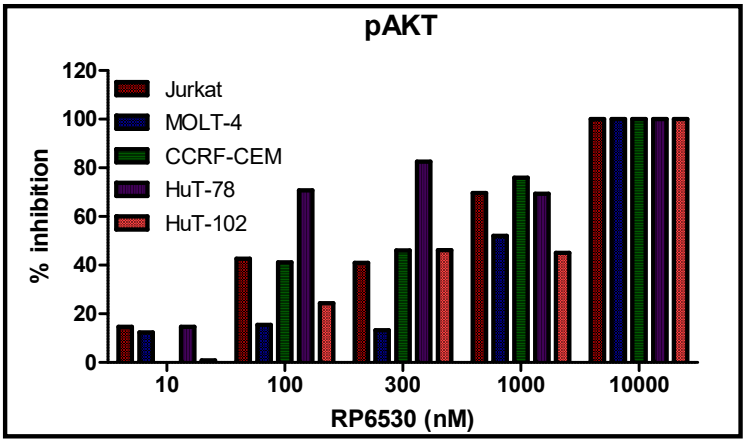


Table 1: Inhibition of leukemic cell growth

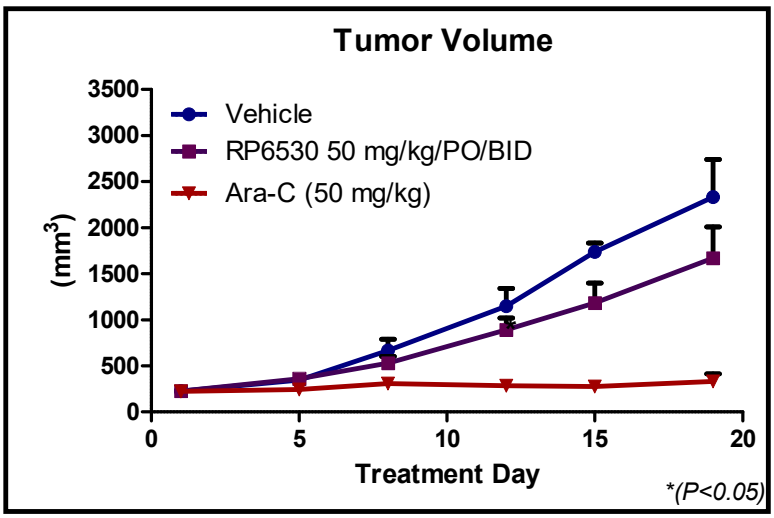
Cell Line	Disease	Cell Type	Organ	GI_{50} (nM)
Daudi	Burkitt's Lymphoma	B lymphoblast	Peripheral Blood	8424
KG-1	Acute Myelogenous Leukemia	Macrophage	Bone Marrow	1741
MM-S	immunoglobulin A lambda myeloma	B lymphoblast	Peripheral Blood	1180
Raji	Burkitt's Lymphoma	B lymphoblast	Maxilla	6937
SU-DHL	Diffuse large cell lymphoma	Anaplastic large cell lymphoma	Pleural Effusion	2519
TOLEDO	Diffuse large cell lymphoma/Non-Hodgkin's B-cell lymphoma	B lymphocyte	Peripheral Blood	3480
CCRF-CEM	Acute lymphoblastic leukemia	T-llymphoblast	Peripheral Blood	7632
Jurkat	Acute T-cell leukemia	T lymphocyte	Peripheral Blood	2077
MOLT-4	ALL	T lymphoblast	Peripheral Blood	3024
HuT-78	Sezary Syndrome	Cutaneous T-lymphoblast	Peripheral Blood	4643
HuT-102	Lymphoma/Mycosis Fungoides	Cutaneous T-lymphoblast	Peripheral Blood	2239

1.3.2 In Vivo Activity

Xenograft

In vivo efficacy of RP6530 was evaluated in a subcutaneous mouse MOLT-4 xenograft model[29] representative of human T-cell acute lymphoblastic leukemia. Oral administration of 50 mg/kg/BID RP6530 over a 18-day period resulted in a significant delay in tumor growth[28].

Figure 4. RP6530 In vivo efficacy



Ex-Vivo Pharmacology

RP6530 inhibited pAKT in primary CTCL cells (Figure 5) with an EC50 of 198.2 nM30. Additionally, the compound caused a dose-dependent induction in apoptosis[29] (Figure 6).

Figure 5: Induction of pAKT in Patient Derived Cells

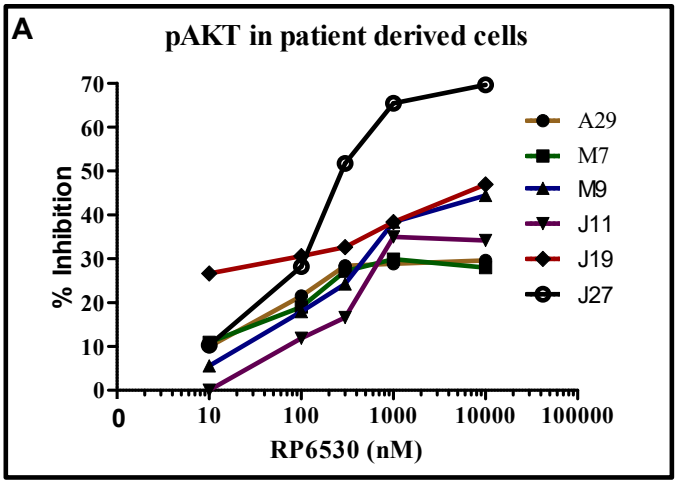
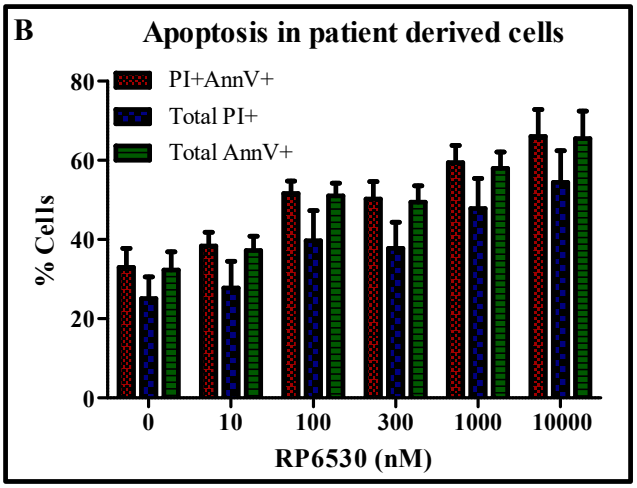


Figure 6: Induction of Apoptosis in Patient Derived Cells



1.3.3 Toxicology

To assess the safety and toxicity of RP6530 a 28-day repeat dose study with a 14-day recovery period was conducted in Rat and beagle dogs, to evaluate the potential reversibility of findings and to support the use in humans.

Once daily oral administration (by Gavage) of RP6530 was well tolerated in rat at dose levels of 5, 20, and 100 mg/kg/day for 28 days. At the terminal euthanasia (Day 29/30) thyroid gland enlargement was a test article-related gross pathology finding in males at 100 mg/kg/day. Follicular cell hyperplasia in the thyroid glands and hepatocellular hypertrophy in the liver were test article-related histopathology findings in males and females at 100 mg/kg/day. Following the 14-day recovery period (Day 43), test article-related findings observed at Day 29/30 were diminished or absent. Target organ effects were observed at levels of 100 mg/kg/day and consisted of thyroid and liver. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 20 mg/kg/day and the Highest Non-Severely Toxic Dose (HNSTD) in the rat[30].

Toxicokinetics of RP6530 were characterized in plasma of male and female rat after a single and repeat dose administration for 28 days. Peak concentrations were achieved between 0.5 and 4.0 h post dose with terminal t1/2 ranging from 2.04 to 6.18 h. Increase in half-life was observed with increasing doses, with no significant accumulation.

Once daily oral administration (as Capsule) of RP6530 was well tolerated in dogs at dose levels of 3, 10 and 30 mg/kg/day. At terminal euthanasia (Day 30/31), small thymuses correlating with decreased organ weight and lymphoid depletion were observed in males of the 10 and 30 mg/kg/day and females of the 30 mg/kg/day groups. Following the 14-day recovery period (Day 44), no test article-related gross pathology or organ weight changes were observed. The liver was identified as a target organ at 30 mg/kg/day in males and females. Based on these results, the no NOAEL was 10 mg/kg and the HNSTD was 30 mg/kg/day for the dog[31].

Toxicokinetics of RP6530 were characterized in plasma of male and female dog after single and repeat dose administration for 28 days. Peak concentrations were achieved between 1.6 and 8.5 h post dose with terminal t1/2 ranging from 1.98 to 9.37 h. Increase in half-life was observed with increasing doses, with no significant accumulation.

Based on the favorable results of pre-clinical and toxicological studies, this first-in-man study is being undertaken to explore the safety, efficacy, and MTD/optimal dosing of RP6530 in patients with haematolgical malignancy in compliance with ICH GCP guidelines.
Refer to the RP6530 Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

1.3.4 Clinical experience

In human, RP6530 is being evaluated in two ongoing clinical trials: *A Phase I Dose Escalation Study Evaluating the Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory Hematologic Malignancies* ***(European study: Protocol Number RP6530-1301)*** and *A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma* ***(USA study: Protocol number RP6530-1401)****. In addition, an open label, randomized, single dose, crossover study was undertaken to evaluate food effects on relative bioavailability of RP6530 administered in fasting and fed conditions in healthy volunteers (Protocol no:* **RP6530-1501**).

In the European study, RP6530 has been safe and well tolerated up to 1200 mg BID and 800 mg TID. There have been no dose-limiting toxicities (DLT). In the US study, a total of 19 patients were treated at 200 mg BID (n=4), 400 mg BID (n=4), 800 mg BID (Fasting) (n=5) and 800 mg BID (Fed) (n=6) in dose escalation part of the study. RP6530 demonstrated acceptable safety and tolerability profile up to 800 mg BID (fasting). Reported SAEs were assessed not related to RP6530 but attributed to the disease under study/concomitant disease conditions. Three DLTs (transaminitis, neutropenia and skin rash each) were reported in RP6530 800 mg BID (fed) cohort, therefore this dose is defined as exceeding MTD. RP6530 800 mg BID (Fasting) is considered as a MTD dose in patients with T-cell lymphoma.

1.3.5 Clinical pharmacokinetics

In the European study, maximum systemic exposures assessed by AUC0-t (r2 = 0.99) as determined on Cycle 1/Day 1 (C1D1) at 25, 50, 100, 200, 400, 600, 800, 1200 mg BID, 600 and 800 mg TID. Dose related exposure observed across the doses. On Day 29, no accumulation observed. Steady state pharmacokinetic parameters of RP6530 as determined on Cycle 2/Day 1 (C2D1) revealed no accumulation. Similar findings were reported in US study. The healthy volunteer (food effect) study showed that administration of RP6530 after a high-fat meal increases the bioavailability of RP6530.

1.4 Rationale

1.4.1 Rationale for the Trial

The δ isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly implicated in various hematologic malignancies. The γ isoform is associated with T-lymphocytes and neutrophils; there appears to be a significant synergy rather than a redundancy between the two

isoforms in various leukemias and lymphomas. As T-cell lymphomas (both CTCL and PTCL) are unmedical need, dual targeting of PI3K δ/γ therefore is strongly implicated as an intervention strategy in leukemia/lymphomas that are hard to treat by conventional means. RP6530 is a highly specific and orally available, PI3K δ and γ inhibitor with nanomolar inhibitory potency, and several fold selectivity over the alpha and beta isoforms. Inhibition of PI3K δ and/or γ signaling with RP6530 in numerous non-clinical assays has demonstrated:

- Potent inhibition of Anti-IgM induced human B-cell proliferation;
- Potent inhibition of PI3Kδ and γ dependent CD63 surface expression in human whole blood basophils;
- Potent reduction of AKT phosphorylation in several B-cell and T-cell cell-lines.
- In vivo efficacy in a mouse T-cell leukemia Xenograft model
- Ex-vivo activity in malignant patient derived primary CTCL cells
- High oral bioavailability and high clearance of RP6530 support twice daily dosing in humans.

1.4.2 Rationale for the Starting Dose

Based on the favorable results of pre-clinical and toxicological studies, this first-in-man, Phase I, 3+3 dose escalation study has been initiated in Europe in patients with relapsed and/or refractory hematologic malignancies (Study RP6530-1301). Patients received starting dose of 25 mg BID (50 mg/day).

As the safety of 200 mg BID was established in European study, it was reasonable to consider 200 mg BID dose as the starting dose in proposed Phase I study in relapse/refractory T-cell lymphoma. Presence of anti-tumor activity will be a real benefit to this patient population who have limited choice of treatment.

2. TRIAL OBJECTIVES

2.1 Primary Objective

- To evaluate the safety and the maximum tolerated dose (MTD) of RP6530 in patients with relapsed/refractory T-cell lymphoma (CTCL/PTCL).
- To evaluate the pharmacokinetic (PK) effects of RP6530.

2.2 Secondary Objectives

- To examine the pharmacodynamic (PD) effects of RP6530.
- To assess and the overall response rate (ORR) and duration of response (DoR) in patients with relapsed/refractory T-cell lymphoma.

2.3 Exploratory Objectives

- Correlation of treatment outcomes with biomarkers which include but are not limited to quantitative and qualitative measurements of cytokines, chemokines and aberrations indicative of PI3K function and RP6530 efficacy.

3. TRIAL DESIGN

3.1 Trial End Points

3.1.1 Primary Endpoint

- AE, SAE, clinically significant AE and dose limiting toxicities (DLT).
- PK parameters (including $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, λ_z, and $t_{½}$) of RP6530

3.1.2 Secondary end points

- Inhibition of pAKT by RP6530.
- ORR as defined as sum of CR and PR rates; and DoR.

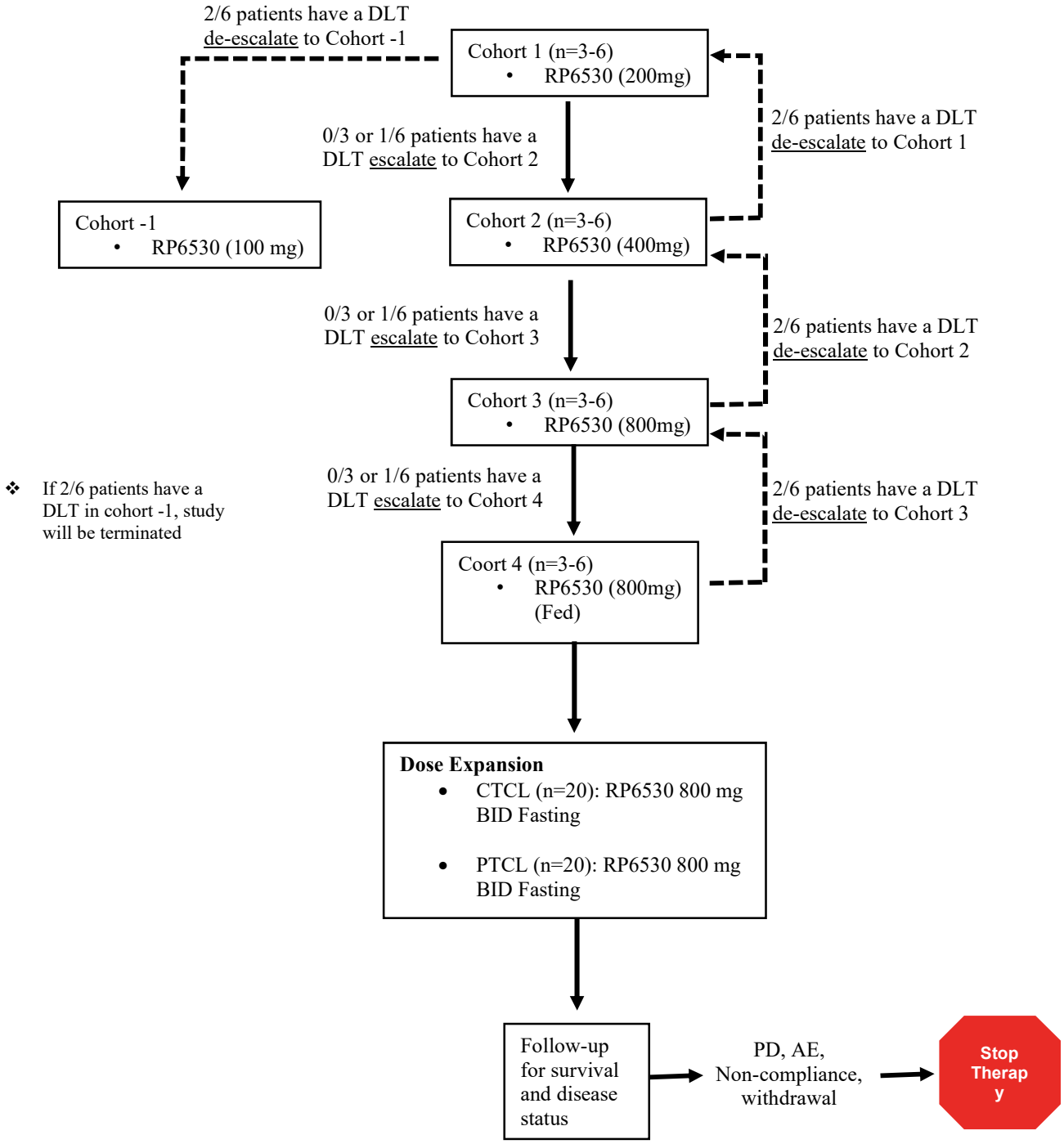
3.1.3 Exploratory end points

- Correlative biomarkers (e.g. serum cytokines and chemokines).

3.2 Design of trial

This is a two part Phase 1/1b study. The first part is a Phase 1 dose escalation, 3+3 design, open-label, MTD determination study of RP6530 in patients with relapsed/refractory T-cell lymphoma (PTCL/CTCL). The second part is Phase 1b, dose expansion, open label study to be conducted once the MTD/optimal dose has been confirmed in dose escalation phase. 20 patients of each indication will be enrolled (20 for PTCL and 20 for CTCL). RP6530 will be administered orally twice a day in 28-days cycle in absence of disease progression, unacceptable toxicity, or withdrawal from treatment.

Figure 7: Study design and dose escalations



3.3 Part 1: Phase 1, dose Escalation

3.3.1 Dose escalation procedure

Sequential dose escalation will begin with Cohort 1. A minimum of three patients of either CTCL or PTCL will be entered into each opened dose level cohort. The first cohort of patients will receive RP6530 200 mg twice a day (BID). Dose levels will be increased in successive increments according to the dose escalation scheme in the **Table 2.** Dose escalation will continue until the MTD/optiomal dose has been identified or as determined by the DRG based on the available safety, PK and/or efficacy data. Dose determination will be documented appropriately.

Table 2: Dose Escalation Schedule

Dose Level	RP6530 PO BID	Dosing recommendation	Patients (n)
1*	200 mg BID	Fasting	3-6
2	400 mg BID	Fasting	3-6
3	800 mg BID	Fasting	3-6
3a	800 mg BID	After food	3-6

*If not tolerated or DLT occurs in over 33% of patients treated, a dose level of Dose Level -1 (i.e. 100 mg BID) will be tested.

** In fasting cohorts, patients will fast 2 hours prior to study drug administration and 1 hour after administration. In Fed cohort (After food), patients to take study drug after food (30 minutes after breakfast and dinner).

Notes:

- The first 28-days of safety follow up data as confirmed by the Investigator(s), and C1D1 PK data is essential for dose-escalation decisions.
- Dose escalation may occur if no patient within a three-patient cohort experiences a DLT as defined in Section 6.6. If one of three patients within a 3-patient cohort experiences a DLT, an additional three patients will be treated at the same dose level. If one of six patients within a dose level experiences a DLT, dose escalation will continue. If two or more of six patients within a dose level experience a DLT, that dose level will be defined as exceeding MTD, **no further dose escalation will occur.** The previous dose level will be considered the MTD and will be expanded to further elucidate safety, to define PK, and to evaluate efficacy.
- If two of the first 3 patients in a cohort experience a DLT, that dose level will be defined as exceeding MTD, no further dose escalation will occur. The previous dose level will be considered the MTD and will be expanded to further elucidate safety, to define PK, and to evaluate efficacy.
- The actual number of dose cohorts explored will depend upon the MTD and the safety profile observed during the conduct of the trial. Intermediate dose levels and dosing schedules may be explored if deemed appropriate.
- An optimal dose is defined as the threshold dose at which the study drug is clinically active / efficacious (shows complete response or partial response) in a specific disease population and is at or below the maximum tolerated dose.

3.3.2 Intra-subject dose escalation

Individual patients may be considered for treatment at a dose level of RP6530 higher than the dose to which they were initially assigned. For a patient to be treated at a higher dose level of RP6530, the patient must not have experienced a DLT at the assigned dose and tolerated the lower dose for at least one cycle of therapy. The patient must have undergone a disease evaluation and been found appropriate to continue on study. The new higher dose must be a dose that has completed evaluation and has not exceeded the MTD. There is no limit to the number of times a patient may have their dose of RP6530 increased. However, the rules remain the same as listed above. At the discretion of the treating investigator(s), the dose escalation may be done in patient who received lower doses (de-escalation) due to safety reason.

3.3.3 Alternative Dosing Cohorts

Depending on the nature and the timing of the toxicities encountered and the pharmacokinetic data from continuous daily dosing of RP6530, alternative dosing regimens and schedules may be examined. If in the opinion of the DRG, observed toxicities (DLTs and/or non-dose limiting adverse events of concern) are likely to have resulted from a continuous exposure to the study drug or cumulative effect, alternative dosing regimens or schedules may be explored. The DRG will determine the alternative schedule, based on PK data, nature and timing of toxicities, and the required recovery periods for the observed toxicities encountered. Dose escalation would proceed with an alternative schedule to determine the MTD/optimal dose.

3.4 Part 2: Phase 1b, dose expansion

Once the MTD/optimal dose has been confirmed, patients who complete the Dose Escalation Phase will be permitted to enter the expansion cohorts (Phase Ib). Additional CTCL and PTCL patients may be enrolled to reach a maximum of 58 patients (including the Phase I patients) in each of the CTCL and PTCL groups.

Table 3: Dose Expansion Schedule

Dose Level	RP6530 PO BID	Patients (n)
CTCL	MTD (RP6530 800 mg Fasting)	20
PTCL	MTD (RP6530 800 mg Fasting)	20

3.5 Randomization and Blinding

This is a non-randomised, open label study.

3.6 Investigational Medicinal Product

3.6.1 Dosage form and Strenghts

Investigational Product	Dosage form and strength	Manufacturer
RP6530	200 mg and 400 mg tablets	Alembic Pharmaceuticals and WuXi AppTec. Shanghai

Additional information can be found in the current RP6530 Investigator Brochure.

3.6.2 Labeling, Packaging and Supply

RP6530 will be made available by XXXXXXXXXXXX and XXXXXXXX. Shanghai and supplied through Rhizen Pharmaceuticals SA to the study site. All trial drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for RP6530 are included in the RP6530 Investigator's Brochure and on the product label.

3.6.3 Preparation and Administration of Investigational Products

RP6530 will be available as 30 tablets per bottle. At each visit, patients will be dispensed sufficient RP6530 drug supplies until the next visit. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented.

RP6530 tablets will be self-administered by the patients. RP6530 will be administered orally twice daily. In case of fasting cohorts, patients should swallow RP6530 tablets whole with a full glass (approximately 8 ounces) of water in a fasting state. In fed cohorts, RP6530 tablets will be self-administered orally twice daily after food (30 minutes after breakfast and dinner). RP6530 tablets should NOT be crushed/opened or chewed.

3.6.4 Accountability of Investigational Products

The PI (or designee) is responsible for accountability of all used and unused trial drug supplies at the site.The study monitor will verify receipt of investigational product at the site during monitoring visit(s), and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All trial drug inventories must be made available for inspection by the monitor, sponsor representatives and regulatory agency inspectors upon request.

Returned or expired trial drugs can be destroyed according to local institutional policy with sponsor pre-approval of a site-specific destruction policy. Certificate(s) of destruction must be filed at the site and in Trial Master File.

3.6.5 Precautions and Risks Associated with Investigational Products

Monitoring of liver enzymes and levels of TSH, T3, and T4 in subjects receiving RP6530 is recommended based on target organ toxicity. Patients should be monitored for increased ALT/AST, skin rash, neutropenia as these events are reported with RP6530. Monitor patients for signs and symptoms of these events and interrupt RP6530 for Grade 3 or higher event. In addition, enteritis (colitis), pneumonia/pneumonitis as these events are reported with other PI3K inhibitors.

RP6530 may cause serious infections that may include sepsis and other infections. Monitor patients for signs and symptoms of infection and interrupt RP6530 for Grade 3 or higher infection. RP6530 elicit no photo instability upon exposure to ultraviolet (UV) radiations. However, in absence of an in-vitro data, possibility of phototoxicity with RP6530 cannot be ruled out. Therefore, patients should be warned about the possible photosensitivity and advised to be careful with the UV exposure while on RP6530 treatment. Patients should be recommended to wear loose-fitting clothes that protect skin from sun exposure, in case they need to be outdoors. If sunburn like reaction or skin eruption occurs, patients should contact study physician.

RP6530 800 mg BID (Fasting) is considered as a MTD dose in patients with T-cell lymphoma. Refer to the current Investigator Brochure for details of the risks associated with the use of RP6530, and instructions on how to manage patients.

RP6530 demonstrated moderate to high inhibition of CYP3A4 enzymes. Therefore, concomitant administration of RP6530 with CYP3A4 substrates (e.g. calcium channel blockers, warfarin, carbamazepine, macrolide antibiotics, lovastatin, simvastatin, terfenadine) may reduce clearance of these drugs increasing the risk of adverse events.

Similarly, as RP6530 is metabolized by CYP3A4/5 and CYP2C9, there is possibility of drug interaction with inhibitors or inducers of CYP3A4 and CYP2C9. If concomitant treatment of these drugs are clinically warranted, careful observation of the patient is advised. Raised INR has been reported with concomitant warfarin administration. Therefore, use of heparin or warfarin is generally avoided. Low molecular weight heparin (LMWH) is advised for prophylaxis and treatment of venous thrombosis. In absence of reproductive toxicity and genotoxicity data, the study participants should be advised to follow post treatment contraceptive measures.

3.7 The expected duration of subject participation and follow-up

The expected duration of subject participation in the study will be 8 months. Treatment will be continued in patients experiencing clinical benefit for 2 years unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI/Co-PI after consultation with Sponsor on case to case basis.

The study will end when **all ongoing subjects** have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, wheichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up.

3.8 Study stopping rules

Stopping rule for dose escalation:
The DRG (PI, Co-PI, Medical Monitor and Sponsor Representative) will be in charge of reviewing safety data following the final treatment dose (Day 28 of Cycle 1) of the last patient in each cohort, and will decide whether or not it is possible to proceed to the next cohort according to the dose escalation procedure described in Section 3.3 In order to ensure safety and limit toxicity for enrolled patients, dose modifications will be performed according to the procedure described in Section 6.7.

Suspension of Patient Enrollment:
In the event of one (1) death attributed to the study drug, study accrual will be suspended pending further investigation, and will only be resumed at the recommendation of the DRG. The DRG will have discretion to terminate the trial if an additional death occurs that can be attributed to the study drug.

Phase Ib:
Once the MTD/optimal in the Phase I dose-escalation have been established, the Phase Ib expansion part of the study will open after review of safety, PK and/or efficacy data by the DRG.

The DRG will continue to monitor toxicity for serious adverse events as well as for toxicity trends that may be of concern at interval of 3 months from initiation of expansion cohort to completion of the study. Toxicity will be monitored across cohorts combined together, as the expansion will be done at the specific dose (either MTD or optimal dose). The DRG may recommend to the Sponsor early termination of a study group if none of the first 10 patients achieve an objective response (PR or >), or </= 6 of the first 20 patients achieve an objective response (PR or >) by the second efficacy assessment performed before or on Cycle 8/Day 1 (C8D1).

Study stopping:
Sponsor reserves the right to terminate the study in the interest of patient safety, for non-compliance with the protocol, lack of recruitment or any other administrative reasons. The sponsor and PIs will notify the regulatory authority and respective IRB respectively if the trial terminates early, with a justification for the early termination.

4. SELECTION AND WITHDRAWAL of SUBJECTS

4.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in this clinical trial:

1. Histologically confirmed T cell Non-Hodgkin Lymphoma (T-NHL) as approved by the Medical Monitor or PI/Co-PI.
2. Disease status defined as:
   - Refractory to or relapsed after ≥ 1 prior treatment lines.
   - Patients who are not eligible for transplantation or any standard and / or approved therapy known to be life prolonging or life saving (patients who may be eligible for transplantation or any standard and /or approved therapy but have declined therapy, or in the investigators opinion based on the patient's condition, an investigational therapy may benefit more than existing approved therapies are eligible for the study).
3. Patients with a measurable or evaluable disease.
   - In case of radiologically measurable lesions, the longest diameter should be ≥ 2cm in PTCL patients.
   - PTCL patients with non-measurable lesions but assessable disease (e.g. marrow disease without other radiographically measurable disease) can be enrolled in dose-escalation phase as approved by PI/Co-PI.
4. Adequate organ system function, defined as follows:
   - Patients with haemoglobin levels and/or neutrophil and platelet counts under these values will be eligible in case abnormalities are due to tumor dissemination or infiltration and according to physician's discretion and under his direct responsibility.
     a. Hemoglobin ≥8 g/dL
     b. Absolute neutrophil count (ANC) ≥0.75 x 10^9/L
     c. Platelets ≥50 x 10^9/L
   - Total bilirubin ≤1.5 times the upper limit of normal (ULN)
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or 5 x the ULN if known liver involvement.

- Creatinine ≤ 2.0 mg/dL OR calculated creatinine clearance ≥50 mL/min as calculated by the Cockcroft-Gault method

5. ECOG performance status ≤2.
6. Life expectancy of at least 12 weeks.
7. Patients must be ≥18 years of age.
8. Ability to swallow and retain oral medication.
9. Female patients who are not of child-bearing potential or female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential, and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530. A barrier method of contraception must be included.
10. Male patients willing to use adequate contraceptive measures throughout the study period and for 12 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530.
11. Willingness and ability to comply with trial and follow-up procedures.
12. Ability to understand the nature of this trial and give written informed consent.

Note: The EORTC classification of CTCLs will be used to classify patients. CTCL includes other variants other than MF (e.g. Gamma delta cutaneous T-cell lymphoma or subcutaneous or panniculitic like T-cell lymphoma and CD8 positive T-cell lymphoma). PTCL includes patients with predominantly nodal disease (systemic involvement) but some patients (e.g.. AITCL or ATCL) may have skin lesions. Patient having both skin and node lesions will be placed into one of the group (CTCL or PTCL) as approved by PI/Co-PI.

There are a number of FDA-approved drugs for relapsed/resistant CTCL and/or PTCL. These include romedepsin, denileukin diffitox, vorinostat, bexarotene, mechlorethamine gel, pralatrexate and belinostat. Investigator should make accommodations for the use of such approved therapies prior to enrollment on the study.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from trial entry:

1. Any cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) in the last 3 weeks or the last 5T1/2 of the agent, whichever is shorter. Limited palliative radiation <2 weeks.
2. Autologous hematologic stem cell transplant within 3 months of study entry. Allogeneic hematologic stem cell transplant within 12 months. Active graft-versus-host disease.
3. Active HBV, HCV or HIV infection.
4. Use of an investigational drug in the last 4 weeks prior to the first dose of RP6530
5. Treatment with GS-1101 (CAL-101, idelalisib), IPI-145, TGR-1202 or any drug that specifically inhibits PI3K/ mTOR (including temsirolimus, everolimus), AKT or BTK Inhibitor (including Ibrutinib) in last 6 months.
6. Patient has received wide field radiotherapy (including therapeutic radioisotopes such as Yttrium-90) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to starting RP6530 or has not recovered from side effects of such therapy.

7. Ongoing immunosuppressive therapy including systemic corticosteroids (prednisone or equivalent ≤10 mg daily allowed as clinically warranted). Patients are allowed to use topical or inhaled corticosteroids.
8. Known history of drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension.
9. Patients with uncontrolled Diabetes Type I or Type II (HbA1c >8% assessed locally).
10. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV [see Appendix B])
    - QTcF > 470 msec
    - Angina not well-controlled by medication
    - Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months
    - Active or uncontrolled severe infections requiring IV antibiotics
    - Patients with hemophilia or even Von Willebrand's disease should be excluded.
11. Herbal preparations/medications must be discontinued 7 days prior to first dose of study drug.
12. Presence of other active cancers, or history of treatment for invasive cancer ≤ 3 years. Patients with stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e. non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
13. Women who are pregnant or lactating.
14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
15. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.
16. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.

4.3 Discontinuation from Trial Treatment

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

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values related to drug toxicity
- Consent withdrawal
- Patient requests to discontinue treatment
- Pregnancy (See Section 6.5)
- Inability of the patient to comply with trial requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (at the investigator's discretion)
- Non-compliance/lost to follow-up
- Discontinuation of the study by the Sponsor

If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described in **Section 6.6.1** that patient will be replaced. Decision of discontinuation should be taken on case to case basis after discussion with medical monitor.

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

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

5. TREATMENT OF SUBJECTS

5.1 Administration of RP6530

RP6530 will be dosed continuously twice a day in 28-days cycle. The dose and schedule of RP6530 will be determined during the dose escalation phase of the study. RP6530 will be self-administered by the patient. Tablet (s) of relevant strenghs should be taken at approximately the same time each day. Patients should be instructed to swallow RP6530 tablets as a whole with a full glass (approximately 8 ounces) of water in a fasting state (fasting cohorts); and with food in fed cohorts (30 minutes after breakfast and dinner); and should not chew or crush them. Patients will fast 2 hours prior to study drug administration and 1 hour after administration. On days of study visits, the morning dose to be adminsisted at the clinic. ***In dose expansion, RP6530 should be administered in a fasting state.***

If a dose of RP6530 is missed, it should be taken as soon as possible the same day. If it is missed for the entire day, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented. No routine prophylactic antiemetics or premedications will be given. However, these medications may be administered for symptoms when they occur, and may be given prophylactically afterwards.

5.2 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

- Use of erythropoietin replacement or bisphosphonates is considered supportive care, and their use is permitted if initiated >2 weeks prior to trial treatment.

- Use of antimicrobial or anti-viral prophylaxis can be used according to local standard practice; PCP and Zoster prophylaxis is strongly recommended unless there is known adverse events from the prophylactic therapy in the individual.
- Initiation or escalation of growth factor therapy (erythropoietin, GM-CSF, G-CSF) is not allowed during the first month of study treatment. However, patients who have been on stable erythropoietin or darbepoetin therapy for two weeks preceding trial treatment may remain on the same dose during the first month. Growth factor therapy, if initiated in the first month for the treatment of study drug **related** AE (e.g. RP6530 related neutropenia), such patients will be discontinued. Growth factor therapy is allowed after the first month as are changes in the dose level of erythropoietin and darbepoetin.
- Transfusions may be given, based on standard criteria and clinical judgment.
- Patients are permitted to receive palliative radiation therapy on study after Cycle 1 at the discretion of the treating physician for existing bone lesions if there is no evidence of progressive disease elsewhere.
- Prophylactic antiemetics will be withheld until the patient has experienced ≥ CTCAE grade 1 nausea or vomiting. The patient may then receive prophylactic antiemetics at the discretion of the investigator. Premedications for hypersensitivity (allergic reactions) will not be administered prophylactically.
- If in the opinion of the investigator the risk of tumor lysis syndrome (TLS) is significant, allopurinol may be given prophylactically.
- RP6530 demonstrated moderate to high inhibition of CYP3A4 enzymes. Therefore, concomitant administration of RP6530 with CYP3A4 substrates (e.g. calcium channel blockers, carbamazepine, macrolide antibiotics, lovastatin, simvastatin, terfenadine) may reduce clearance of these drugs increasing the risk of adverse events. Similarly, as RP6530 is metabolized by CYP3A4/5 and CYP2C9, there is possibility of drug interaction with inhibitors or inducers of CYP3A4 and CYP2C9. If concomitant treatment of CYP3A4 substrates are clinically warranted, careful observation of the patient is advised, particularly during treatment initiation. Raised INR has been reported with concomitant warfarin administration. Therefore, use of heparin or warfarin is generally avoided. Low molecular weight heparin (LMWH) is advised for prophylaxis and treatment of venous thrombosis.

5.3 Prohibited Medications

The following treatments are prohibited while on clinical trial:

- Other investigational drug treatments or study participation, radiation therapy (except as described above), hormonal therapy for cancer, cancer immunotherapy or other biologic therapy excluding trial drugs.
- Herbal preparations/medications are not allowed throughout the trial. Examples include: St. John's wort, Kava, ephedra (ma huang), ginko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications at least 7 days prior to the first dose of study drug.

Note: ***Discontinuation of patient who received concomitant/prohibited medication will be taken by the PI/Co-PI in consultation with Medical Monitor on case to case basis, after evaluating the clinical benefit and acceptable/minimal clinical risk***

5.4 Procedures for monitoring subject compliance.

Subjects will be asked to maintain a diary to record drug administration. Subjects will be asked to bring any unused study drug to the research center at their next visit. Research personnel will count and record the number of used and unused study drug tablets at each visit and reconcile with the subject diary. The study coordinator will question the patient regarding adherence to the dosing regimen, record the number of tablets and strengths returned, the date returned and determine treatment compliance before dispensing new medication to the study patient. Compliance below 80% will require counseling of the patient by study site personnel.

6. ASSESSMENT OF SAFETY

6.1 Adverse Events

The PI is responsible for collecting and reporting adverse events (see 6.1.2). It is Sponsor responsibility to report relevant SAEs to the applicable regulatory body.

6.1.1 Definitions of Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. All Grade 3 and grade 4 AEs irrespective of causality constitute clinically significant AE.

6.1.2 Recording of Adverse Events

All adverse events of any patient during the course of the trial will be reported in the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). If the adverse event is serious, it should be reported immediately to Sponsor. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs (i.e., AEs that occur prior to assignment of trial treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs regardless of seriousness or relationship to RP6530 (study drug), spanning from the first dose of study drug until 30 calendar days after the last dose of study drug, discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded in the CRF. The data review group (DRG), comprise of PI/Co-PI, Medical Monitor and sponsor representative, will be constituted to review safety data on ongoing basis.

6.1.3 Handling of Adverse Events

All adverse events resulting in discontinuation from the trial should be followed until resolution or stabilization. Patients must be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the adverse event or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical

record and as a comment on the CRF. After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

6.2 Adverse Event/Serious Adverse Event Causality Assessment

Causality is assessing the relationship of the trial treatment to the adverse event. For this study, the causality assessment will be categorized as related and not related.

Related: All toxicities should be considered to be related to RP6530 unless there is a clear alternative explanation.

Not related: If there is no temporal association, or another etiology has been identified as the cause, or the trial treatment cannot be implicated based upon the current information.

6.3 Serious Adverse Events

6.3.1 Definitions of Serious Adverse Events

The definitions of serious adverse events (SAEs) are given below. The principal investigator is responsible for ensuring that all staff involved in the trial are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per Cheson et al. 2007 Revised Response Criteria for Malignant Lymphoma), should not be reported as a serious adverse event.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial), does not require reporting as a serious adverse event to the Sponsor.

6.3.2 Serious Adverse Event Reporting by Investigators

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

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to Sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the signing of the informed consent form through the 30-day follow-up period after the last trial treatment. Sponsor/sponsor representative must be notified of all SAEs, regardless of causality, within 1 day of the first knowledge of the event by the investigator.

To report an SAE, the SAE Report Form should be completed with the necessary information. All SAEs occurring from the signing of consent until 30 calendar days of last trial treatment must be reported to the Sponsor as SAEs on the SAE Report and followed until resolution (with autopsy report if applicable).

Deaths and other SAEs occurring >30 calendar days after last trial treatment that are deemed 'possibly' or 'probably' related to RP6530 must be reported as SAEs on the SAE Report within 1 day of first knowledge of the event by the treating physician or research personnel (with an autopsy report if available).
Deaths occurring >30 calendar days after last trial treatment and not attributed to trial treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate CRF.

The SAE report should be sent to the Sponsor/Sponsor representative via fax or e-mail. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual. Transmission of the SAE report should be confirmed by the site personnel submitting the report. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Sponsor as soon as it is available; these reports should be submitted using the SAE Report Form.
Investigators must report SAEs and follow-up information to their responsible Institutional Ethics committee (IEC) according to the policies of the responsible IEC.

6.3.3 Sponsor SAE Reporting Requirements

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

Sponsor/sponsor representative is responsible for reporting unexpected fatal or life-threatening events associated with the use of the trial drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event. The

Sponsor will report all related unexpected SAEs including non-death/non-life-threatening related unexpected SAEs associated with the use of the trial medications to the FDA by a written safety report within 15 calendar days of notification. Reporting to the IRB/IEC will be done according to institutional policy.

6.4 Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE CRF. Avoid colloquialisms and abbreviations. All AEs, including those that meet SAE reporting criteria, should be recorded on the AE CRF; AEs that meet the definition of an SAE should additionally be reported following the procedures noted in above sections.

6.4.1 Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Coordinating Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE CRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

6.4.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the SAE Report Form and/or the AE CRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded at once with highest grade of severity on a SAE Report Form and/or AE CRF.
A recurrent AE is one that occurs and resolves between patient evaluation timepoints, and subsequently recurs. All recurrent AEs should be recorded separately on an SAE Report Form and/or AE CRF.

6.4.3 Abnormal Laboratory Values

Any grade 3 or 4 laboratory abnormalities or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value(s) should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant CRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE CRF.

6.4.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of disease will be recorded on the "Trial Discontinuation" CRF.

All other on-trial deaths, regardless of attribution, will be recorded on an SAE Report and expeditiously reported to the Spoonsor.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE report and Adverse Event page of the CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the CRF Adverse Event page.

6.4.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. (see Section 06.3.1)

6.4.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the General Medical History CRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

6.4.7 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to pregnancy section 6.5 for specific instructions.

6.4.8 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include new lesions of the original cancer. Symptoms of metastasis or the new lesions itself should not be reported as an AE/SAE, as they are considered to be disease progression.

6.4.9 Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the sponsor or reporting physician considers the study treatment contributed to the deterioration of the condition, the deterioration should be considered lack of efficacy and not an AE.

6.5 Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously.

Pregnancy, Abortion, Birth Defects/Congenital Anomalies:

Female patients who are not of child-bearing potential (see Appendix C) or female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment are eligble for the study. Female patients of child-bearing potential (see Appendix C), and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530. A barrier method of contraception must be included.

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

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

If an investigator suspects that a patient may be pregnant after the patient has been receiving trial drug(s), the trial drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the trial drug(s) must be immediately and permanently stopped, the patient must be discontinued from the trial, and the investigator must notify the Medical Monitor and Sponsor Representative as soon as possible. If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and faxed to the Sponsor.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

RP6530 Overdose

Symptomatic and non-symptomatic overdose must be reported in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within one day) using the corresponding screens in the CRF, and following the same process described for SAE reporting, if the overdose is symptomatic.

6.6 Dose-Limiting Toxicity

Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE).

All toxicities should be considered to be related to RP6530 unless there is a clear alternative explanation. A toxicity will be considered dose-limiting if it occurs during the first cycle (4-weeks) treatment with RP6530 and is considered related to RP6530. Dose-limiting toxicities will be defined as the following:

- Hematological DLTs:
  - Grade 4 anaemia
  - Grade 4 neutropenia (absolute neutrophil count [ANC] <500/µL) for >7 days, or Grade ≥3 febrile neutropenia (ANC <1000/µL with fever >38.5ºC [101ºF]
  - Grade 4 thrombocytopenia for >7 days, or grade ≥3 thrombocytopenia associated with Grade >2 bleeding
- Non-Hematological DLTs:
- Grade ≥3 non-hematologic toxicity with exception of:
  - Grade ≥3 diarrhea or nausea that does not resolve to ≤ Grade 2 within 48 hours despite treatment; and
  - If ≥1.5 ULN of bilirubin or >3 ALT/AST elevation that does not resolve to ≤ Grade 1 within 7 days.
- Treatment delay of ≥14 days due to unresolved toxicity.
- Non-hematologic toxicity of Grade 2 (at any time during treatment) that, in the judgment of the DRG, is dose-limiting.
- For certain toxicities such as laboratory assessments without a clear clinical correlate (e.g. lipase increase without signs of a clinical pancreatitis) a discussion within DRG may take place if this AE should be assessed as DLT necessitating dose reduction.

6.6.1 Determination of Dose-Limiting Toxicity

The patient population used for determination of MTD will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. Minimum safety requirements will be met if, **during Cycle 1 of treatment**,

- Patient receives at least 80% of planned doses of RP6530 doses or received RP6530 for the first 21-days continuously;
- Patient completes all required safety evaluations (at least for three visits after the first dose);
- Patiet is observed for at least 28 days following the first dose of RP6530 in case of related adverse event.

Patients who experience a DLT will be considered evaluable regardless of the number of doses received.

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

6.6.2 Maximum Tolerated Dose (MTD)

The MTD is the highest dose at which ≤1 of 6 patients experience a DLT during 1 cycle (28 days) of therapy. If 2 or more patients in a dosing group experience a DLT, the MTD has been exceeded.

6.7 Dose Modifications

Patients should be assessed for toxicity using the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) grading scale. Patients who experience either a DLT or an adverse event meeting DLT criteria (that occurs after the DLT assessment window)

will be allowed to delay dosing in order to recover from the toxicity. Patients may resume RP6530, provided that the toxicity has resolved to Grade ≤2 or baseline. If study drug is delayed >2 weeks because of an adverse event, treatment may not be resumed until the strategy has been discussed with the Medical Monitor and continuation of treatment has been agreed upon.

At the discretion of the Investigator, a dose re-escalation may be permitted for patients who were dose reduced upon resuming RP6530. Holidays from study drug are discouraged. Any patient in whom similar toxicity recurs at the reduced dose should be discontinued from further RP6530 treatment. Exceptions to this discontinuation rule, on the basis of ongoing clinical benefit and acceptable/minimal clinical risk), a patient may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and with approval from the Medical Monitor.

6.7.1 Criteria for Starting RP6530 New Cycle

Criteria for continuing treatment beyond the first cycle will be at the discretion of the treating Investigator. In the absence of unacceptable toxicities or disease progression, patients may continue treatment with RP6530 as long as:

- Absolute neutrophil count has returned to baseline, or >750/μL. Platelet count is ≥50,000/μL.
- Recovered from grade 3-4 non-hematologic toxicity to grade 1 or baseline (excluding alopecia). Treatment may be delayed for up to 2 weeks to recover from toxicity.
- No clinical or radiographic evidence of disease progression.
- If treatment is delayed > 2 weeks, because of an adverse event, treatment may not be resumed until the strategy has been discussed with the Medical Monitor and continuation of treatment has been agreed upon.

6.7.2 RP6530 Dose Modifications for Hematologic Toxicity

Table 4: Dose Modifications for Hematologic Toxicity

Worst CTCAE Grade Toxicity	Action to be Taken
HEMATOLOGIC	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1.0-1.5 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 0.5-1.0 x 10^9/L)	Hold* dose until resolved to ≤ Grade 2 or baseline, consider growth factor support, then reduce by 1 dose level. If the ANC is <1 X 10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity, and the dose shall not be modified as long as ANC >0.5 X 10^9/L.
Grade 4 (ANC < 0.5 x 10^9/L)	Hold* dose until resolved to ≤ Grade 2 or baseline, consider growth factor support, then reduce by 1 dose level. If the ANC is <1 X 10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity, and the dose shall be held until resumption of baseline ANC is achieved; consider growth factor support, reduce drug by one dose level.

Grade 3 Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Hold* dose until resolved to ≤ Grade 2 or baseline, consider growth factor support, then reduce by 1 dose level***. If the ANC is <1 X 10^9/L (1000/µL) before therapy, the patient is not evaluable for toxicity, and the dose shall not be modified as long as ANC >0.5 X 10^9/L.
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level.
Grade 3 (PLT < 50-25 x 10^9/L)	Hold** dose until to ≤ Grade 2 or baseline, then reduce by 1 dose level if warranted***.
Grade 4 (PLT < 25 x 10^9/L)	Hold** dose until to ≤ Grade 2 or baseline, then reduce by 1 dose level if warranted***.

* If study drug is delayed >2 weeks because of an adverse event, treatment should not be resumed until the strategy has been discussed with the Medical Monitor and continuation of treatment agrred upon.
** Patient receiving concomitant medication (e.g. anticoagulants, antiplatelets, aspirin, or low molecular weight heparin) must be discussed with the Medical Monitor for continued management.
*** Further dose reduction can be done in consultation with medical monitor.

6.7.3 RP6530 Dose Modifications for Non-Hematologic Toxicities

The dose reduction guidelines for non-hematologic toxicities are shown in Table 5.

Table 5: Dose Modifications for Non-Hematologic Toxicities

NON-HEMATOLOGIC	Action to be Taken
Renal*	If serum creatinine >3 x baseline or >3 x ULN, hold dose until ≤ grade 1. Monitor serum creatinine at least twice a week until resolution to ≤ grade 2, and then at least one week until it resolves to ≤ grade 1
Hepatic*	Please refer the algorithm for dose modification. (***Annexure M***).
Cardiac	If a QTcF >500 msec has been demonstrated, hold dose: For all patients with a new QTcF >500 msec, occurring at any time during the study as identified by the investigator, an immediate evaluation of that ECG will be obtained and confirmed. The patient will be monitored hourly with ECGs until the QTcF <500 msec and the QTcF has returned to <30 msec from baseline. Immediate attention to potassium and magnesium and other clinical factors such as oxygenation and ischemia will be addressed. A plasma sample will be drawn to assess the concentrations of study drug, magnesium and potassium at the time when the QTcF is first noted to be >500 msec.
OTHER NON-HEMATOLOGIC	**Action to be Taken**
Grade 1 or 2	None
Grade 3 CTCAE	Hold* dose until toxicity Grade ≤1 , then reduce by 1 dose level.
If toxicity remains grade 3 toxicity for longer than 2 weeks	Contact medical monitor

If grade 3 toxicity lasts 2 weeks and resolves to ≤ grade 1	Hold* dose until toxicity Grade ≤1
Exception	Grade ≥3 diarrhea or nausea that does not resolve to Grade ≤2 within 48 hours of treatment, reduce one dose level.
Recurrence of grade 3 of toxicity	Reduce one dose level or more or discontinue treatment after discussion with medical monitor*
Grade 4 CTCAE	Hold* dose until toxicity Grade ≤1 , then reduce by 1 dose level
Recurrence of grade 4 toxicity	Discontinue study drug

* If study drug is delayed >2 weeks because of an adverse event, treatment should not be resumed until the strategy has been discussed with medical monitor and continuation of treatment agreed upon.

Note: *In the event of **unrelated** hematological/non-hematological toxicity (e.g. toxicity due to underlying disease condition or co-morbidity), the dose modification or dose delay will be done at the discretion of PI/Co-PI after evaluating the safety of the patient and need for dose modification.*

7 ASSESSMENT OF EFFICACY

7.1 Specification of the efficacy parameters.

PTCL patients will be evaluated by PI according to the International Working Group Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007 (Appendix E)[32]. Bone marrow disease alone may be used for disease assessment. In this case, response would be CR or non-CR only, determined by the morphology of repeat bone marrow biopsy.

CTCL response and progression will be evaluated by PI according to the Response Criteria in Mycosis Fungoides and Se´zary Syndrome by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force ofthe European Organisation for Research and Treatment of Cancer (EORTC) criteria (Appendix K)[33]. Patients with non-measurable lesions but assessable disease will be evaluated using appropriate diagnostic modality as approved by PI/Co-PI. Similarly, patient having both skin and node lesions will be evaluated appropriately to assess the response. Additional measurement/evaluations will be performed for a specific indication if deemed necessary.

7.2 Response Evaluations and Measurements

At baseline PTCL and CTCL will be staged and diagnosis will be confirmed by an expert hematologist and dermato-oncologist respectively. Clinical assessments will include ECOG performance status, lymph nodes, organomegaly, and “B” symptoms. The staging of PTCL and CTCL patients will be done according to Ann Arbor (Appendix F) and ISCL/EORTC criteria (Appendix H) [34] respectively.

CTCL: Recommended evaluation/initial staging of the patient with CTCL (MF /SS) is given Appendix G. For the definition of patch, plaque, and tumor should be as outlined in ***Appendix I***. For study eligibility, the histopathologic diagnosis should be confirmed by a skin biopsy. These patients will have half body global and up to 5 selected representative index lesions photographed at baseline, at C3D1, End of treatment (EOT), at PR/CR/PD and as required as per the discretion of PI/Co-PI. The pre-treatment evaluation and scoring of response parameters (Refer

Appendix L) can be done at baseline/screening. These scores will constitute the comparison values for all response measurements during the study. For skin scoring, the modified Severity Weighted Assessment Tool (mSWAT) will be used. For local index lesion skin scoring, Composite Assessment of Index Lesion Severity **(*Appendix J*)** will be used. ***Appendix K*** will be used for the definition of response in skin, lymph node, viscera and blood of patients with MF/SS. CTCL patients (sub-cutaneous or panniculitic like) with subcutaneous lesions which cannot be measured by mSWAT will be assessed by change in their positron emission tomography (PET)- computed tomography (CT) PET-CT avid lesions.

In CTCL patients with other than presumed stage IA disease, or selected patients with limited T2 disease and the absence of adenopathy or blood involvement, computed tomography (CT) scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. MRI may be substituted if clinically indicated, but the modality chosen to evaluate each individual patient should be the same throughout the duration of the study.

PTCL: In these patients, bone marrow biopsy and CT scan of the thorax, abdomen, and pelvis will be performed. Bulky disease will be defined by the presence of tumor mass >5cm in the longest diameter. CT scans of the chest, abdomen and pelvis are required only for patients with measureable disease. Other scans may be performed (e. g, head CT) if clinically indicated or if the area is a site of known disease. PET-CT will be used to assess response in FDG-avid histologies. The product of the perpendicular diameters of a single node can be used to identify progressive disease.[35] CT scans will be also performed at the end of treatment if the patient is discontinued for reasons other than disease progression and a previous assessment has not been performed within 30 days.

In both indications, the disease will be assessed by PI at baseline and at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the disctetion of PI/Co-PI. All patients who discontinue study drugs will have an End of Treatment (See Appendix D) visit within 30 days from the last dose of study drug. The frequency outlined is the minimum required for study participation. Patients who progress according to the corresponding criteria will receive no further treatment. Patients who respond to the treatment (i.e., CR, PR or SD) may remain on trial. All disease specific assessments are to be completed as applicable to disease type. The modality chosen should be the same throughout the duration of the study.

8 TRIAL ASSESSMENTS AND TREATMENT

8.1 Overview

A cycle of treatment is scheduled to last 4 weeks (28 calendar days). Patients will visit the study center according to the schedule of assessments shown in Appendix D. In dose expansion, all

visits to be performed on monthly interval; patients will be visiting hospital on Day 1 of each cycle (e.g. Day 1 of Cycle 1, Cycle 2, and Cycle 3… etc).

Multiple procedures may be scheduled at the same time point relative to RP6530 dosing. Priority should be given to PK collection at the time specified followed by collection of PD samples. Vital signs should be performed prior to specimen collections.

8.2 Screening

The informed consent must be obtained ≤28 days prior to initiation of treatment before any protocol-specific procedures are performed. Patient registration will be done as per site's practice. Sites will assign a patient identification number and dose level. Screening assessments described in Appendix D will be collected, reviewed, and determined to be acceptable by the site PI or designee after obtaining informed consent and ≤7 calendar days prior to the initiation of treatment. If these initial examinations are obtained within 72 hours (or as otherwise noted) of Cycle/1 Day 1, they do not have to be repeated. Rescreening can be done at the discretion of PI. Scans to document measurable or evaluable disease should be performed ≤4 weeks prior to initiation of treatment.

During screening active Active HBV, HCV or HIV infection should be ruled out. To be considered negative for active infection will be used:

- HBV: HBc antibody should be negative or if HBc antibody is positive, HBVDNA should be undetectable
- HCV: HCV antibody should be negative or if HCV antibody is positive, HCVDNA should be undetectable
- HIV: HIV antibody should be negative. (HIV 1/ 2 antibody should be negative unless positive result is considered false positive by PI)

8.3 Laboratory Investigations

The CBC plus differential, platelets, biochemistry test, PT/INR will be perfomed as mentioned in **Annexure D.** Blood drawn for these tests will be specified in informed consent form (ICF). The investigations will be performed at local laboratory. The additional details will be provided in laboratory manual.

1. All laboratory investigations should preferably be done in fasting condition prior to administration of RP6530.
2. TSH, free T3 and free T4 should be performed as part of thyroid function testing and recorded in the eCRF. Total T3 and total T4, if performed as a Standard of Care (SOC), it should be recorded as an additional test in the eCRF.
3. Serum bicarbonate should be performed as part of the electrolyte assessment. If carbon dioxide (CO2) is performed as SOC, it should be recorded as an additional test in the eCRF.
4. Blood Urea Nitrogen (BUN) is preferred; if not available, Urea may be tested as per institutional practice.
5. PT/INR: PT should be recorded in seconds. Both PT and INR results are to be entered in the eCRF field separated.
6. Routine urinalysis should include at minimum pH, urobilinogen, ketones, glucose, protein, RBC, WBC, nitrites and caste. Additional parameters should be included if clinically relevant per Investigator judgement.

8.4 12-Lead Electrocardiograms

There is no preclinical evidence of QTc liability with RP6530 to date. In Dose escalation, a single ECG will be performed at screening and C1D1 pre-dose. Post-dose ECGs will be performed in conjunction with the 1 hr, 2hr and 4hr post-dose PK collection on C1D1; and on C1D8 (pre-dose), C1D15 (pre-dose), and C1D22 (pre-dose). On C2D1, ECGs will be obtained pre-dose and then one hour post-dose coinciding with the PD collection. In Dose Expansion, a single ECG will be performed at screening, C1D1 pre-dose and C2D1 pre-dose and one hour post-dose.

Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. All ECGs will be performed on local equipment.

8.5 Bone Marrow Biopsy/Aspiration

PTCL: Patients entering the study with low grade lymphoma must have a morphology and flow cytometry performed ≤3 months prior to study entry and/or to confirm a complete response. Patients with high grade lymphoma must have a morphology and flow cytometry performed ≤28 days prior to study entry and/or to confirm a complete response.

Patients without measurable disease but assessable disease (e.g. marrow disease without other radiographically measurable disease) will have have a bone marrow biopsy at screening /baseline and on C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/or to confirm a complete response.

CTCL: Patients with predominantly blood involvement (as confirmed by flow cytometry) will have a bone marrow biopsy at screening /baseline (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response occurring at all other sites. Specific molecular exams for some particular malignancies will be performed according to institutional diagnostic guidelines.

8.6 Skin Biopsy

CTCL: skin biopsy should be performed at screening, on C3D1 (± 7 days) and/or to confirm a complete response at the most indurated area if only one biopsy. Immunophenotyping to include at least the following markers: CD3, CD4, CD7, CD8 and Ki67. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered. Clonality of TCR gene rearrangement will be performed as part of standard of care and will be an optional. This information will be sought from patient's previous report.
PTCL: Skin assessment will be performed at the time of screening in case of skin lesion.

8.7 Radiological Evaluations

A CT scan (chest, abdomen, pelvis) and other radiological evaluations (X-RAY/MRI/Ultrasound) will be provided by the patients at the time of screening prior to therapy. PET-CT will be used to assess response in FDG-avid histologies. These evaluations should have been performed within 28 days of screening. Efficacy evaluation would be done at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days). Patients will be restaged after radiological evaluations. Refer section 7.2 for additional details.

8.8 Pharmacokinetic Assessments

Extensive PK sample collection is applicable to Dose Escalation. Pre-dose sample will be collected in Dose Expansion at the start of each cycle (e.g. C1D1, C2D1,…). No PK assessments are required beyond Cycle 8. The PK parameters (including $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, λ_z, and $t_{½}$) of RP6530 following will be assessed by analysis of RP6530 plasma concentrations during the dose escalation phase of the study. Exploratory analysis will be performed if deemed essential. Please refer Annexure D for PK blood samples. Plasma samples will be collected and stored at -70 °C at the clinic and shipped to Bioanalytical Laboratory: NorthEast Bioanalytical Laboratories, 925 Sherman Avenue, Hamden, CT 06514, USA. See laboratory manual for PK processing instructions.

8.9 Pharmacodynamics

The PD samples (to estimate pAKT) will be performed on C1D1 (pre-dose and 1 hr later), C1D8 (pre-dose) and C1D22 (pre-dose); C2D1 (pre-dose) and C3D1 (pre-dose) and/ at EOT in five sezary syndrome (SS) patients at MDACC only. pAKT will not be performed in dose expansion. The analyses for pharmacodynamic biomarkers (inhibition of pAKT) are exploratory, and will not be used to guide treatment decisions. The results may be pooled with data from other studies to generate hypotheses to be tested in future studies. Whole blood samples will be collected, cells will be extracted and stored at -70°C, until analyzed. See laboratory manual for PD processing instructions.

8.10 Correlative Assessments/Exploratory Biomarkers

Correlative serum biomarkers (e.g. sIL2R CTACK (PTCL); CD30 (MF), IL-31 and IL-32 (CTCL)) will be performed at screening, C3D1 (pre-dose and 1 hr later); at EOT and/ or to confirm a response. Blood will be collected for these biomarkers, serum aliquots will be prepared and shall be stored at below -70^0C until analysis. The decision to analyse the serum samples will be taken at later stage only if required or deemed necessary by the investigator/sponsor.

The analyses of correlative biomarkers are exploratory evaluation, and will not be used to guide treatment decisionsin the dose escalation and expanded cohort of the study. See laboratory manual for biomarker processing instructions.

8.11 Archived Tumor Tissue

Archival tissues will be collected from all patients, if the tissue sample available. Institutional procedure will be followed for processing and archieval of tumor tissue.

8.12 Trial Treatment Period

In Dose Escalation, patients will visit the study center weekly (± 1 day) in during cycle 1 and 2 for safety assessment. All visits should occur as close as possible to the protocol specified time. Complete listings of the assessments that will be performed at each visit during the trial treatment period are specified in Appendix D. Patients will return to the study center weekly during cycles 1 and 2 for safety assessments. During Cycles 3 and 4 patients will return to the study center on Days 1 (± 3 day) and Day 15 (± 3 day) of each cycle for assessments and study drug. Patients continuing on study after Cycle 4 will return to the study center on Day 1 (± 3 day) of each subsequent cycle for study drug and safety assessments. In Dose Expansion, all visits to be performed on monthly interval.

8.13 Response Assessment

Response will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the disctetion of PI/Co-PI. Patients with progressive disease or unacceptable toxicity should be discontinued from the trial; patients with stable disease or response to therapy will continue treatment. The assessments to be performed at this time are specified in Appendix D.

8.14 End of Trial Treatment

Patients are permitted to continue treatment with RP6530 until disease progression, or the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the trial physician. Follow-up evaluations required after treatment ends are specified in Appendix D. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no trial treatment is administered, that visit may fulfill the End of Trial Treatment Visit.

After withdrawal from or completion of protocol treatment, patients must be followed for any new adverse events for 30 calendar days after the last dose of trial drug.

8.15 Early Patient Termination / Patient Withdrawal

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol (see Appendix D). If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described in Section 6.6.1, that patient will be replaced.

9 STATISTICAL CONSIDERATIONS

The sections of the Statistical Considerations described the statistical methods to be used to analyze the safety and efficacy as described in the objectives. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how censoring procedures will be applied to time to event related variables as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

9.1 General Considerations

This is an open-label, Phase I, dose-escalation study of the PI3K δ/γ inhibitor RP6530. This trial is designed to determine the MTD (or recommended dose) to support further clinical studies, and preliminary information on the safety profile and PK profile and anti-tumor activity of RP6530 given as a single agent.

9.2 Determination of Sample Size

This trial will enroll up to 58 patients at 5-10 sites. The actual number of dose cohorts will depend upon the MTD/ optimal dose (or recommended dose) .

9.3 Statistical Analyses

All statistical analyses will be performed using SAS 9.1 or higher.

9.3.1 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for continuous variables, and frequencies and percentages for categorical variables.

9.3.2 Safety Analyses

The safety population will include all patients who will receive at least one dose of study medication. The safety endpoints will include:

- Incidence of DLTs
- Incidence of AEs and AEs considered to be drug-related
- Incidence of grade 3 and grade 4 AEs
- Incidence of SAEs
- Laboratory values
- ECG/vital signs

The safety endpoints will be listed and/or summarized by dose cohort. No inferential statistical analyses will be performed.
The analyses of safety will be based on the frequency of adverse events and their severity for patients in each portion who received at least one dose of study treatment. Worst toxicity grades per patient will be tabulated for select adverse events and laboratory measurements by using NCI CTCAE criteria v4.0.

9.3.3 Efficacy Analyses

Two populations will be used in the efficacy analyses, Intent-to-Treat (ITT) and Per Protocol (PP) populations. The ITT population will include all safety population who provide efficacy assessment. PP population will include all ITT population without major protocol violations.
The efficacy endpoints will include:

- Overall response rate (ORR)
- Duration of Response (DoR)

These variables will be analyzed/summarized based on the ITT population as well as the PP population as appropriate. The percentages of CR, CR+PR, and CR+PR+SD will be presented, as will the median duration of response. The 95% confidence intervals of these percentages may also be presented.
Additional analyses may also be performed as appropriate.
These analyses will be performed from time to time for presentation/publication purposes.

9.3.4 Pharmacokinetic Analyses

The following PK parameters will be derived:

- AUC, C_{max}, T_{max}, $T_{1/2}$

These variables will be summarized by n, mean, standard deviation, median, minimum, and maximum by dose. The geometric means will also be presented for AUC and C_{max}.

10 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline, and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

10.1 IRB/IEC Approval

The trial protocol, ICF, IB, available safety information, patient documents (e.g., subject diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB/IEC for ethical review and approval if required by local regulations, prior to the trial start.

The PI/Sponsor/CRO and/or designee will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB/IEC trial review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/IEC.
Safety updates for RP6530 will be prepared by the Sponsor or its representative as required, for submission to the relevant IEC.

10.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.
Safety updates for RP6530 will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

10.3 Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

10.4 Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
The informed consent form will be submitted for approval to the IEC that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the US FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the signed informed consent formwill be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the patient's consent to continue participation in the trial should be obtained.

10.5 Confidentiality

10.5.1 Patient Confidentiality

Confidentiality of patient's personal data willbe protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of following:
a. What protected health information (PHI) will be collected from patients in this trial; b. Who will have access to that information and why; c. Who will use or disclose that information; d. The information collected about the research trial will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the trial; e. Whether the authorization contains an expiration date; and f. The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IEC direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify patients on the CRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the CRF or database. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

10.5.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the site database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, the site shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

11 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

11.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.
If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of Rhizen Pharmaceutical. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IEC at the investigator's facility for the board's approval.

Amendments specifically involving change to trial design, risk to patient, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB/IEC at the investigator's facility.

The amendment will be submitted formally to the FDA by the Sponsor as applicable, after IRB/IEC approval and specifically when an increase to dosing or patient exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.
Items requiring a protocol amendment with IRB/IEC and/or FDA approval include, but are not limited to, the following:

- Change to trial design
- Risk to patient
- Increase to dose or patient exposure to drug
- Subject number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the trial design or the potential risks to the patients, their consent to continue participation in the trial should be obtained.

11.2 Documentation Required to Initiate Trial

Before the trial may begin, documentation required by US FDA will be provided by the Sponsor. Documents at a minimum required to begin a trial in the US include, but are not limited to: a signature-authorized protocol and contract; a copy of the official IRB approval ofthe trial and the IRB members list; current Curricula Vita for the principal investigator and any associate investigator(s) who will beinvolved in the trial; indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory; original Form FDA 1572 (Statement of Investigator), appropriately completed and signed; a copy of the IRB-approved consent form containing permission for audit by representatives of Sponsor, the IRB, and the FDA; financial disclosure forms for all investigators listed on Form FDA 1572; site qualification reports, where applicable; verification of Principal Investigator acceptability from local and/or national debarment list(s).

12 DATA HANDLING AND RECORD KEEPING

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be

included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and trial staff are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or Investigator Site File (ISF)) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IRB/IEC approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents

The Investigator shall maintain adequate records of drug disposition, case histories and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., CRFs and medical records), all original, signed informed consent forms, and copies of all CRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the investigator(s)/institutions(s) when the trial-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the trial, both site and sponsor should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to sponsor. The investigator must obtain the sponsor written permission before disposing of any records, even if retention requirements have been met. All trial files will be maintained by the Sponsor/Sponsor Representative/CRO throughout the trial, and will be transferred to the Sponsor at the conclusion of the trial.

12.1 Data Collection

The data will be captured in Case Record Form (CRF). The CRF is clinical trials data management tool that provides investigational sites a standardised and validated, remote, electronic data capture system for the collection of clinical trial data. All data requested on the CRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the CRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The principal investigator will sign and date each casebook attesting to his/her responsibility for the quality of all data included therein, and that the data represent a complete and accurate record of each subject's participation in the study.

Clinical data management will be performed in accordance with applicable standards. Data cleaning procedures will be performed with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events, medical history and concomitant medications will be coded using industry standard dictionaries (MedDRA and WHO Drug).

12.2 Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections by the sponsor, government regulatory authorities, the Sponsor or its representative(s) of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.
Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities, the sponsor or its representative(s). At the Sponsor's discretion Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

12.3 Quality Assurance and Quality Control

Each trial site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

12.4 Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

Inclusion of the investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the investigator of the results of the trial conducted at research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any site Confidential Information from all publications.

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10 PI3Kα Enzyme Assay (Study No. IVT-6530-HPI3K-A-29)
11 PI3Kβ Enzyme Assay (Study No. IVT-6530-HPI3K-B-30)
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13 Anti-IgM induced human B cell proliferation (Study No. IVT-6530-BCP-41)
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15 PDGF induced AKT Phosphorylation in 3T3 cells (Study No. IVT-6530-PAA-34)
16 LPA induced AKT Phosphorylation in 3T3 cells (Study No. IVT-6530-LAB-34)
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14. APPENDIX

Appendix A. ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	**Descriptions**
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

Appendix B: New York Heart Association (NYHA) Classifications

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Contraceptive Guidelines and Pregnancy

Women Not of Childbearing Potential are Defined as Follows:

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL] 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 5 T1/2 (48 hrs) plus an additional 4 weeks 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 subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that patient.
4. Use of a combination of any two of the following (a+b):
   a) Placement of an intrauterine device (IUD) or intrauterine system (IUS).
   b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

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

- Oral contraception, injected or implanted hormonal methods are not allowed as RP6530 may potentially decrease the effectiveness of hormonal contraceptives.
- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Appendix C: Contraceptive Guidelines and Pregnancy (Cont.)

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

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, for 5 T1/2 (48 hrs) plus additional 12 weeks after stopping treatment and should not father a child in this period.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Rhizen Pharmaceuticals SA within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to Rhizen Pharmaceuticals SA. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Rhizen Pharmaceuticals SA study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

Appendix D: Schedule of Assessments (Dose Escalation and Dose Expansion)

PART 1: DOSE ESCALATION

Cycle		Cycle 1				Cycle 2				Cycle C3		Cycle C4		**C5**	**C6**	**C7**	**C8**	**EOT[25]**
Day	**D-28 to 0**	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D15	D1	D1	D1	D1	D1
Window period		±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	+30
Study Days	**D-28 to 0**	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	197	-
Dose escalation visits	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROCEDURE																		
Informed Consent[1]	X																	
Demographics[2]	X																	
Medical history[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X				X				X		X		X	X	X	X	X
LABORATORY TEST/EVALUATIONS																		
Complete blood count[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry panel I[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry panel II[9]	X	X		X		X				X		X		X	X	X	X	X
Serology (HIV, HBV, HCV)	X																	
PT/INR[10]	X	X		X		X				X		X						X
HbA1c	X																	
Urinanalysis (routine)	X	X		X		X				X		X		X	X	X	X	X
Pregnancy test[11]	X	X	**X**	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECGs[12]	**X**	**X**	**X**	**X**	**X**	**X**												
PK blood samples[13]		X	X	X		X	X	X		X	X	X	X	X	X	X	X	
Biomarker samples[14]	**X**									**X**								**X**
PD samples (pAKT)[15]	-	X	X	-	X	X				X								X
Archived tumor tissue[16]	X																	
DISEASE ASSESSMENT																		

Staging[17]	X	-	-	-	-	-	-	-	-	X	-	-	-	X	-	-		X
Radiological Examination[18]	X	-	-	-	-	-	-	-	-	X	-	-	-	X	-	-	X	X
Skin lesion assessment[19]	X	-	-	-	-	-	-	-	-	X	-	-	-	X	-	-	X	X
Skin biopsy[20]	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-
Immunophenotyping and TCR gene rearrangement[21]	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-
Photograph of skin lesion[22]	X	-	-	-	-	-	-	-	-	X	-	-	-		-	-		X
Bone marrow, lymph node biopsy /Aspirate[23]	X	-	-	-	-	-	-	-	-	-[23a]	-	-	-	-[23a]	-	-	-[23a]	X
DRUG ADMINISTRATION & SAFETY EVALUATION																		
Drug administration[24]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Drug dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Drug compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
AE evaluation and reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE evaluation and reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-

Note:

1. Patient should be re-consented in case informed consent is not obtained ≤28 days prior to the initiation of trial treatment.
2. Demographic profile will include age, sex and race.
3. Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies and prior medication (in last 4weeks); and other medical history. Abbreviated history will be taken at all subsequent visits.
4. Vitals will include pulse (sitting/supine); blood pressure (sitting/supine); respiratory rate and oral temperature. (**Note:** Pulse rate and blood pressure can be recorded in sitting **OR** supine position depending on convenience of patient and ease of measurement.)
5. Weight will be measured at all visits. Height to be measured at screening only.
6. Physical examination will include lymph node and systemic examination. Complete physical examination will be done at screening visit. At subsequent visits, abbreviated examination will be done.
7. This will include Hb, complete blood count, reticulocyte count, total leucocyte and differential count and platelet count. Additional investigations will be performed if clinically indicated. Hematology must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated.
8. Chemistry Panel I includes Total bilirubin, ALP, AST, ALT, GGT, LDH and Serum electrolytes (Sodium, Potassium, Bicarbonate/CO_2, Chloride, Magnesium, Phosphorus and Calcium). These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These test will be performed at supplementary visits if clinically indicated.
9. Chemistry Panel II includes blood glucose, urea or blood urea nitrogen, creatinine, albumin, globulin, total protein, Total Cholesterol, TG, LDL and HDL, TSH, free T3 and free T4. These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These test will be performed at supplementary visits if clinically indicated. (**Note:** Total protein and albumin tests will be performed; and globulin will be calculated by deducting value of albumin from total protein)
10. This test must be done ≤7 days prior to initiation of treatment. However, if initial examination is obtained within 72 hours of C1D1; this should not be repeated. This test will be performed at supplementary visits if clinically indicated.
11. This is required for women of child bearing potential. A serum pregnancy test will be performed at screening and baseline (within 72 hours) of dosing. Urine pregnancy test will be performed at other visits as indicated.
12. A single ECG will be performed at screening and C1D1 pre-dose. Post-dose ECGs will be performed in conjunction with the 1 hr, 2hr and 4hr post-dose PK collection on C1D1; and on C1D8 (pre-dose), C1D15 (pre-dose), and C1D22 (pre-dose). On C2D1, ECGs will be obtained pre-dose and then one hour post-dose coinciding with the PD collection. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. All ECGs will be performed on local equipment.
13. PK blood sample collection time points: C1D1 at pre-dose, 0.5, 1, 2, 4, 6, 8 hrs post dose; and C1D8 and C1D15 at predose; C2D1 at pre-dose, 0.5, 1, 2, 4, 6, 8 hrs post dose and C2D8 and C2D15 at pre-dose; C3D1 and C3D15 at pre-dose; C4D1 and C4D15 at pre-dose; Cycle 5 and beyond at predose. Window period for PK sampling will be defined in laboratory manual. No PK assessments are required beyond Cycle 8.
14. Correlative serum biomarkers (e.g. sIL2R CTACK (PTCL); CD30 (MF); IL-31 and IL-32 (CTCL)) will be performed at screening, C3D1 (pre-dose and 1 hr later); at EOT and/ or to confirm a response. Blood will be collected for these biomarkers, serum aliquots will be prepared and will be banked for analysis at later stage.
15. PD samples (pAKT) will be performed on C1D1 (pre-dose and 1 hr later), C1D8 (pre-dose) and C1D22 (pre-dose); C2D1 (pre-dose) and C3D1 (pre-dose) and/ at EOT in 5 sezary syndrome patients.
16. Archival tumor samples will be collected during the trial, if available.
17. Ann-Arbor staging system should be applied in patients with other types of NHL; ISCL/EORTC criteria should be used for CTCL. Patients will be restaged C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT.
18. CT scan (of the chest, abdomen, and pelvis) and other radiological evaluations (X-RAY/MRI/Ultrasound) will be performed at the time of screening within 28 days of screening. PET-CT will be used to assess response in FDG-avid histologies. In CTCL patients with other than presumed stage IA disease, or selected patients with limited T2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET

scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted. PTCL patients will be evaluated according to the IWG Revised Response Criteria for Malignant Lymphoma. Assessment of CTCL response and progression will be evaluated according to the Response Criteria in Mycosis Fungoides and Se´zary Syndrome by the ISCL/EORTC criteria. In both CTCL and PTCL, disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/Co-PI.

19. The assessment of skin lesion will be performed at the time of screening in CTCL patients. The assessments will be performed in PTCL if applicable. For skin scoring, the modified Severity Weighted Assessment Tool (mSWAT) will be used. For local index lesion skin scoring, Composite Assessment of Index Lesion Severity will be used. The disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/Co-PI.
20. Skin biopsy will be performed in CTCL patients at screening, on C3D1 (± 7 days) and/or to confirm a complete response. In CTCL patients, skin biopsy should be performed at the most indurated area if only one biopsy.
21. Immunophenotyping to include at least the following markers: CD3, CD4, CD7, CD8 and Ki67. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered. Clonality of TCR gene rearrangement will be evaluated as part of standard of care and will be an optional. Immunophenotyping will be performed at screening, on C3D1 (± 7 days) and/or to confirm a complete response.
22. CTCL patients will have half body global and up to 5 selected representative index lesions photographed at baseline, at C3D1, End of treatment (EOT), at PR/CR/PD and as required as per the discretion of PI/Co-PI.
23. Bone marrow biopsy: PTCL patients entering the study with low grade lymphoma must have a morphology and flow cytometry performed ≤3 months prior to study entry and/or to confirm a complete response. Patients with high grade lymphoma must have a morphology and flow cytometry performed ≤28 days prior to study entry and/or to confirm a complete response. The lymph node will be required to perform only if the diagnosis is not confirmed at the baseline; and if required at other time points.

23a **PTCL patients without measurable disease but assessable disease** (e.g. marrow disease without other radiographically measurable disease) will have a bone marrow biopsy at screening /baseline and on C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/or to confirm a complete response. CTCL patients with predominantly blood involvement (confirmed by flow cytometry) will have a bone marrow biopsy at screening /baseline (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response occurring at all other sites. Specific molecular exams for some particular malignancies will be performed according to institutional diagnostic guidelines. If bone marrow aspirate is available, it will be processed and shipped according to the laboratory manual. Bone marrow disease alone may be used for disease assessment. In this case, response would be CR or non-CR only, determined by the morphology of repeat bone marrow biopsy.
Post Cycle 8, disease assessments should be performed at 12 weekly intervals (± 7 days), and/ or at the EOT. For example, the appropriate radiological investigation (e.g. CT scan, PET-CT or PET) will be performed in PTCL patients at C11D1, C14D1, C17D1, C20D1, etc. Similarly, mSWAT and/or CAILS and radiological assessment (as required) will be performed in CTCL patients on this schedule.

24. The study drug RP6530 will be administered orally twice a day in 28-days of cycle. The drug administration will be monitored on C1D1 and C2D1 followed by PK evaluation. On other days, the treatment can be administered at home. The treatment period is at least 8 months. Treatment will be continued in patients experiencing clinical benefit for 2 years unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI/Co-PI after consultation with Sponsor on case to case basis.
Beyond Cycle 8, all visits will be monthly. During these monthly visits, RP6530 will be dispensed, medication compliance will be monitored and AEs will be assessed. Efficacy assessments will be done at scheduled visit. An End of treatment (EOT) visit will be performed within 30 days after treatment ends.
    - **Safety assessments:** Ongoing safety assessment is to occur during the monthly visits and AEs are to be reported as required by the protocol. There is no specific safety labs or evaluations to be done as per protocol. As part Standard of care, laboratory evaluations can be done and recorded per Investigator's discretion. Adverse events (AEs, SAEs and deaths) will be recorded and reported for 30 calendar days after discontinuation or completion of protocol-specific treatment. After the 30 day reporting period, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.
    - **Efficacy assessments: D**isease assessments should be performed at 12 weekly intervals (± 7 days), and/ or at the EOT. For example, the appropriate radiological investigation (e.g. CT scan, PET-CT or PET) will be performed in PTCL patients at C11D1, C14D1, C17D1, C20D1, etc. Similarly, mSWAT and/or CAILS and radiological assessment (as required) will be performed in CTCL patients on this schedule.

- **Other assessments:** No other assessments (e.g. PK) are required beyond Cycle 8.
- **Drug dispensing: P**atients will be dispensed 30 days of drug supply at the beginning of each cycle. At each visit, documentation of study drug accountability, compliance and any subject retraining given on proper dose administration must be available in the source notes.

25. All patients will undergo the end-of-treatment assessments listed within 30 days after treatment ends. Patients must be followed for adverse events for 30 calendar days after the last dose of study drug.
26. All visits will be ambulatory except C1D1 and C2D1 that involve extended hospital stay for PK assessment.

PART 2: DOSE EXPANSION										
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**EOT[25]**
Day	**D-28 to 0**	D1	D1	D1	D1	D1	D1	D1	D1	D1
Window period		±1	±1	±3	±3	±3	±3	±3	±3	+30
Study Days	**D-28 to 0**	1	29	57	85	113	141	169	197	-
PROCEDURES										
Informed Consent[1]	X	-	-	-	-	-	-	-	-	-
Demographics[2]	X	-	-	-	-	-	-	-	-	-
Medical history[3]	X	X	X	X	X	X	X	X	X	X
Vitals[4]	X	X	X	X	X	X	X	X	X	X
Height and weight[5]	X	X	X	X	X	X	X	X	X	X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X
LABORATORY TEST/EVALUATIONS										
Complete blood count[7]	X	X	X	X	X	X	X	X	X	X
Chemistry panel I[8]	X	X	X	X	X	X	X	X	X	X
Chemistry panel II[9]	X	X	X	X	X	X	X	X	X	X
Serology (HIV, HBV, HCV)	X	-	-	-	-	-	-	-	-	-
PT/INR[10]	X	X	X	X	X					X
HbA1c	X	-	-	-	-	-	-	-	-	-
Urinalysis (routine)	X	X	X	X	X	X	X	X	X	X
Pregnancy test[11]	X	X	X	X	X	X	X	X	X	X
12-lead ECGs[12]	X	X	X	-	-	-	-	-	-	-
PK blood samples[13]		X	X	X	X	X	X	X	X	
Biomarker samples[14]	X	-	-	X	-	-	-	-	-	X
PD samples (pAKT)[15]	-	-	-	-	-	-	-	-	-	-
Archived tumor tissue[16]	X	-	-	-	-	-	-	-	-	-
DISEASE ASSESSMENTS										
Staging[17]	X	-	-	X	-	X	-	-		X
Radiological Examination[18]	X	-	-	X	-	X	-	-	X	X
Skin lesion assessment[19]	X	-	-	X	-	X	-	-	X	X
Skin biopsy[20]	X	-	-	X	-	-	-	-	-	-

Immunophenotyping and TCR gene rearrangement[21]	X	-	-	X	-	-	-	-	-	-
Photograph of skin lesion[22]	X	-	-	X	-		-	-		X
Bone marrow/ lymph node biopsy /Aspirate[23]	X	-	-	-[23a]	-	-[23a]	-	-	-[23a]	X
DRUG ADMINISTRATION AND SAFETY EVALUATION										
Drug administration[24]	-	X	X	X	X	X	X	X	X	-
Drug dispensing	-	X	X	X	X	X	X	X	X	-
Drug compliance	-		X	X	X	X	X	X	X	-
AE evaluation and reporting	X	X	X	X	X	X	X	X	X	X
SAE evaluation and reporting	X	X	X	X	X	X	X	X	X	X
Concomitant medication	-	X	X	X	X	X	X	X	X	X
Diary evaluation	-		X	X	X	X	X	X	X	-

Foot Notes:

1. Patient should be re-consented in case informed consent is not obtained ≤28 days prior to the initiation of trial treatment.
2. Demographic profile will include age, sex and race.
3. **Medical history:** Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies and prior medication (in last 4weeks); and other medical history. Abbreviated history will be taken at all subsequent visits.
4. **Vitals** will include pulse (sitting/supine); blood pressure (sitting/supine); respiratory rate and oral temperature. (**Note:** Pulse rate and blood pressure can be recorded in sitting **OR** supine position depending on convenience of patient and ease of measurement.)
5. Weight will be measured at all visits. Height to be measured at screening only.
6. **Physical examination** will include lymph node and systemic examination. Complete physical examination will be done at screening visit. At subsequent visits, abbreviated examination will be done.
7. **Complete blood count** will include Hb, complete blood count, reticulocyte count, total leucocyte and differential count and platelet count. Additional investigations will be performed if clinically indicated. Hematology must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated.
8. **Chemistry Panel I** includes Total bilirubin, ALP, AST, ALT, GGT, LDH and Serum electrolytes (Sodium, Potassium, Bicarbonate/CO_2, Chloride, Magnesium, Phosphorus and Calcium). These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These tests will be performed at supplementary visits if clinically indicated.
9. **Chemistry Panel II** includes blood glucose, urea or blood urea nitrogen, creatinine, albumin, globulin, total protein, Total Cholesterol, TG, LDL and HDL, TSH, free T3 and free T4. These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72

hours of C1D1; they do not have to be repeated. These tests will be performed at supplementary visits if clinically indicated. (**Note:** Total protein and albumin tests will be performed; and globulin will be calculated by deducting value of albumin from total protein)

10. **PT/INR** must be done ≤7 days prior to initiation of treatment. However, if initial examination is obtained within 72 hours of C1D1; this should not be repeated. This test will be performed at supplementary visits if clinically indicated.
11. **Pregnancy test** is required for women of child bearing potential. A serum pregnancy test will be performed at screening and baseline (within 72 hours) of dosing. Urine pregnancy test will be performed at other visits as indicated.
12. **ECG:** A single ECG will be performed at screening, C1D1 pre-dose and C2D1 pre-dose and one hour post-dose. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. All ECGs will be performed on local equipment.
13. **PK**: C1D1 at pre-dose, C2D1 at pre-dose, C3D1 at pre-dose; C4D1 at pre-dose; Cycle 5 and beyond at predose. Window period for PK sampling will be 1 hr pre-dose. No PK assessments are required beyond Cycle 8.
14. **Correlative serum biomarkers** (e.g. sIL2R CTACK (PTCL); CD30 (MF); IL-31 and IL-32 (CTCL)) will be performed at screening, C3D1 (pre-dose and 1 hr later); at EOT and/ or to confirm a response. Blood will be collected for these biomarkers; serum aliquots will be prepared and will be banked for analysis at later stage.
15. **PD samples (pAKT):** pAKT is not applicable to dose expansion
16. **Archival tumor samples** will be collected during the trial, if available.
17. **Staging:** Ann-Arbor staging system should be applied in patients with other types of NHL; ISCL/EORTC criteria should be used for CTCL. Patients will be restaged C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT
18. **Radiological assessment:** PTCL: A CT scan (of the chest, abdomen, and pelvis) and other radiological evaluations (X-RAY/MRI/Ultrasound) will be performed at the time of screening within 28 days of screening. PET-CT will be used to assess response in FDG-avid histologies. In CTCL patients with other than presumed stage IA disease, or selected patients with limited T2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted. PTCL patients will be evaluated according to the IWG Revised Response Criteria for Malignant Lymphoma. Assessment of CTCL response and progression will be evaluated according to the Response Criteria in Mycosis Fungoides and Sezary Syndrome by the ISCL/EORTC criteria. In both CTCL and PTCL, disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/CoPI.
19. **Skin lesion assessment**: The assessment of skin lesion will be performed at the time of screening in CTCL patients. The assessments will be performed in PTCL if applicable. For skin scoring, the modified Severity Weighted Assessment Tool (mSWAT) will be used. For local index lesion skin scoring, Composite Assessment of Index Lesion Severity will be used. The disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/Co-PI
20. **Skin biopsy:** Biopsy will be performed in CTCL patients at screening, on C3D1 (± 7 days) and/or to confirm a complete response. In CTCL patients, skin biopsy should be performed at the most indurated area if only one biopsy.
21. **Immunophenotyping** to include at least the following markers: CD3, CD4, CD7, CD8 and Ki67. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered. Clonality of TCR gene rearrangement will be evaluated as part of standard of care and will be an optional. Immunophenotyping will be performed at screening, on C3D1 (± 7 days) and/or to confirm a complete response.
22. **Photograph of skin lesion**: CTCL patients will have half body global and up to 5 selected representative index lesions photographed at baseline, at C3D1, End of treatment (EOT), at PR/CR/PD and as required as per the discretion of PI/Co-PI.
23. PTCL patients entering the study with low grade lymphoma must have a morphology and flow cytometry performed ≤3 months prior to study entry and/or to confirm a complete response. Patients with high grade lymphoma must have a morphology and flow cytometry performed ≤28 days prior to study entry

and/or to confirm a complete response. The lymph node will be required to perform only if the diagnosis is not confirmed at the baseline and if required at other time points.

23a CTCL patients with predominantly blood involvement (confirmed by flow cytometry) will have a bone marrow biopsy at screening /baseline (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response occurring at all other sites. Specific molecular exams for some particular malignancies will be performed according to institutional diagnostic guidelines. If bone marrow aspirate is available, it will be processed and shipped according to the laboratory manual.

24. The study drug RP6530 **800 mg BID in fasting conditions** will be administered orally twice a day in 28-days of cycle. The drug should be administered at hospital during hospital visits. On other days, the treatment can be administered at home. The treatment period is at least 8 months. Treatment will be continued in patients experiencing clinical benefit for 2 years unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI-Co-PI after consultation with Sponsor on case to case basis.

Beyond Cycle 8, all visits will be monthly. During these monthly visits, RP6530 will be dispensed, medication compliance will be monitored and AEs will be assessed. Efficacy assessments will be done at scheduled visit. An End of treatment (EOT) visit will be performed within 30 days after treatment ends.

- **Safety assessments:** Ongoing safety assessment is to occur during the monthly visits and AEs are to be reported as required by the protocol. There is no specific safety labs or evaluations to be done as per protocol. As part Standard of care, laboratory evaluations can be done and recorded per Investigator's discretion. Adverse events (AEs, SAEs and deaths) will be recorded and reported for 30 calendar days after discontinuation or completion of protocol-specific treatment. After the 30 day reporting period, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.
- **Efficacy assessments: D**isease assessments should be performed at 12 weekly intervals (± 7 days), and/ or at the EOT. For example, the appropriate radiological investigation (e.g. CT scan, PET-CT or PET) will be performed in PTCL patients at C11D1, C14D1, C17D1, C20D1, etc. Similarly, mSWAT and/or CAILS and radiological assessment (as required) will be performed in CTCL patients on this schedule.
- **Other assessments:** No other assessments (e.g. PK) are required beyond Cycle 8.
- **Drug dispensing: P**atients will be dispensed 30 days of drug supply at the beginning of each cycle. At each visit, documentation of study drug accountability, compliance and any subject retraining given on proper dose administration must be available in the source notes.

25. All patients will undergo the end-of-treatment (EOT) assessments listed within 30 days after treatment ends. Patients must be followed for adverse events for 30 calendar days after the last dose of study drug.

26. All visits will be ambulatory.

Appendix E: Response Criteria for Malignant Lymphoma

International Working Group Revised Response Criteria for Malignant Lymphoma (Cheson et. al. 2007)

Complete Response (CR):	*The designation of CR requires the following:* • Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. • Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan is positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. • Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan is negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment. • The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma. • If the bone marrow is involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.
Complete Response/Unconfirmed (CRu):	*The use of the above definition for CR and those below for PR eliminates the category of CRu.*

Appendix E. Response Criteria for Malignant Lymphoma (continued)

Partial Response (PR):

The designation of PR requires all of the following:

- At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver, or spleen.
- Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample is positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
  When the bone marrow is involved before therapy and a clinical CR is achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed.
- Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan is positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan is negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Appendix E. Response Criteria for Malignant Lymphoma (continued)

Stable Disease (SD):	*Stable disease (SD) is defined as the following:* • A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]). • Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET. • Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET is negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.
Relapsed Disease (after CR) / Progressive Disease (after PR, SD):	*Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.* • Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation. • At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis. • At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis. • Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion is PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Appendix E. Response Criteria for Malignant Lymphoma (continued)

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Response Assessment:

Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	• FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative • Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	• ≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes • FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site • Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified

Appendix E. Response Criteria for Malignant Lymphoma (continued)

Response Definitions for Clinical Trials (continued)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
SD	Failure to attain CR/PR or PD	• FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • Variably FDG-avid or PET negative; no change in size of previous lesions on CT	—	—
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis • Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Source: Cheson BD, Pfistner B, Malik E, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol. 2007;25:579-86.

Appendix F: Ann Arbor staging system

Stage I
Either of the following means the disease is stage I:

- The lymphoma is in only 1 lymph node area or lymphoid organ such as the thymus (I).
- The cancer is found only in 1 area of a single organ outside of the lymph system (IE).

Stage II
Either of the following means the disease is stage II:

- The lymphoma is in 2 or more groups of lymph nodes on the same side of (above or below) the diaphragm (the thin band of muscle that separates the chest and abdomen). For example, this might include nodes in the underarm and neck area but not the combination of underarm and groin nodes (II).
- The lymphoma extends from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.

Stage III
Either of the following means the disease is stage III:

- The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- The cancer may also have spread into an area or organ next to the lymph nodes (IIIE), into the spleen (IIIS), or both (IIISE).

Stage IV
Either of the following means the disease is stage IV:

- The lymphoma has spread outside of the lymph system into an organ that is not right next to an involved node.
- The lymphoma has spread to the bone marrow, liver, brain or spinal cord, or the pleura (thin lining of the lungs).

Other modifiers may also be used to describe the lymphoma stage:

Appendix G: Recommended evaluation for MF/SS ptients

Recommended evaluation/initial staging of the patient with mycosis fungoides/Sézary syndrome

Complete physical examination including

- Determination of type(s) of skin lesions
  - If only patch/plaque disease or erythroderma, then estimate percentage of body surface area involved and note any ulceration of lesions
  - If tumors are present, determine total number of lesions, aggregate volume, largest size lesion, and regions of the body involved
- Identification of any palpable lymph node, especially those >1.5 cm in largest diameter or firm, irregular, clustered, or fixed
- Identification of any organomegaly

Skin biopsy

- Most indurated area if only one biopsy
- Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered.
- Evaluation for clonality of TCR gene rearrangement

Blood tests

- CBC with manual differential, liver function tests, LDH, comprehensive chemistries
- TCR gene rearrangement and relatedness to any clone in skin
- Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including CD4+/CD7- or CD4+/CD26-)

Radiologic tests

- In patients with T1N0B0stage disease who are otherwise healthy and without complaints directed to a specific organ system, and in selected patients with T2N0B0disease
- with limited skin involvement, radiologic studies may be limited to a chest X-ray or ultrasound of the peripheral nodal groups to corroborate absence of adenopathy
- In all patients with other than presumed stage IA disease, or selected patients with limited T2disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone±FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted.

Lymph node biopsy

- Excisional biopsy is indicated in those patients with a node that is either ≥1.5 cm in diameter and/or is firm, irregular, clustered, or fixed
- Site of biopsy
  - Preference is given to the largest lymph node draining an involved area of the skin or if FDG-PET scan data are available, the node with highest standardized uptake value (SUV).
  - If there is no additional imaging information and multiple nodes are enlarged and otherwise equal in size or consistency, the order of preference is cervical, axillary, and inguinal areas.
- Analysis: pathologic assessment by light microscopy, flow cytometry, and TCR gene rearrangement.

Appendix H: ISCL/EORTC staging of MF and SS patients

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b}(plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node‡	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/µL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

- Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

- ↵* Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

- ↵† Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions1 to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.
- ↵‡ The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Modified ISCL/EORTC Revisions to the Staging of MF/SS

Stage	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1.2	1,2X	0	0,1
IIb	3	0-2X	0	0,1
IIIA	4	0-2X	0	0
IIIB	4	0-2X	0	1
IVA1	1-4	0-2X	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3X	1	0-2

X clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.

Appendix I: Modified Severity Weighted Assessment Tool

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

- NOTE. mSWAT score equals summation of each column line.
- Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.
- ↵* Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
- ↵† Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
- ↵‡ Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Appendix J: Composite Assessment of Index Lesion Severity

Clinical Sign and Degree or Size (scale of 0-8)	Index Lesion				
	1	2	3	4	5
Erythema					
Scaling					
Plaque elevation					
Hypo- or hyperpigmentation					
Lesion size*					
Subtotal					
Total (sum of subtotals)					

- NOTE. Cannot be used as skin assessment in global response score. Suggestions for improvement include using actual size of lesion versus categorical score for size and eliminating pigmentation as a clinical parameter.

- ↵* Lesion size (cm^2): 0: no measurable area; 1: > 0 to ≤ 4; 2: > 4 to ≤ 10; 3: > 10 to ≤ 16; 4: > 16 to ≤ 25; 5: > 25 to ≤ 35; 6: > 35 to ≤ 45; 7: > 45 to ≤ 55; 8: > 55 to ≤ 70; 9: > 70 to ≤ 90; 10: > 90 to ≤ 110; 11: > 110 to ≤ 130; 12: > 130 to ≤ 155; 13: > 155 to ≤ 180; 14: > 180 to ≤ 210; 15: > 210 to ≤ 240; 16: > 240 to ≤ 270; 17: > 270 to ≤ 300; 18: > 300.

Appendix K: Definition of Response in CTCL patients

Response in Skin*

Response	Definition
Complete response	100% clearance of skin lesions[*]
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease[†]	≥ 25% increase in skin disease from baseline or
	New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or
	Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

- NOTE. Based on modified Severity Weighted Assessment Tool score.
- [*] A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides7), the response should be considered a partial response only.
- [†] Whichever criterion occurs first.

Response in Lymph node*

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD[†]	≥ 50% increase in SPD from baseline of lymph nodes or
	Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or
	Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR

Response	Definition
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

- Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

- ↵* Peripheral and central lymph nodes.
- ↵† Whichever criterion occurs first.

Response in Viscera*

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or
	New organ involvement or
	Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

- Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

- ↵* Whichever criterion occurs first.

Response in blood*

Response	Definition
CR‡	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or
	> 50% increase from baseline and at least 5,000 neoplastic cells/μL[36]or
	Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

- Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

- ↵* As determined by absolute numbers of neoplastic cells/μL.
- ↵† If a bone marrow biopsy is performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
- ↵‡ There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
- ↵§ Whichever occurs first.

Appendix L: Body Surface area assessment note for CTCL patients

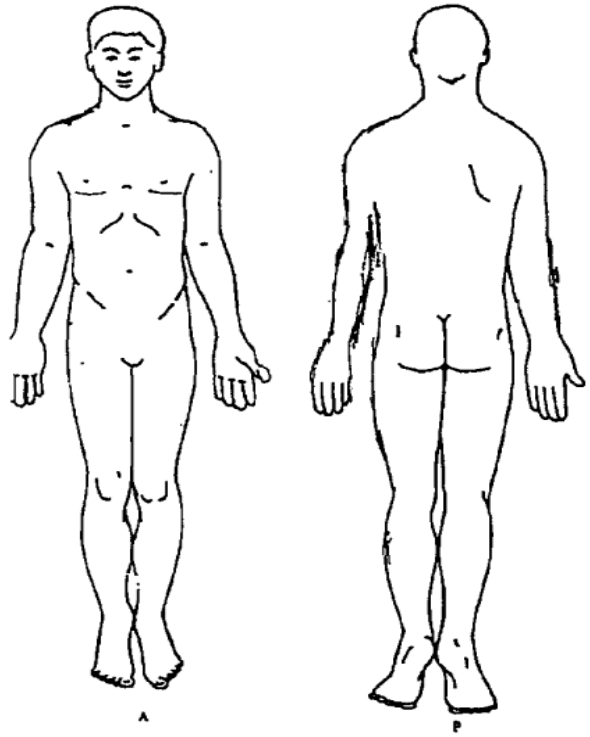
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

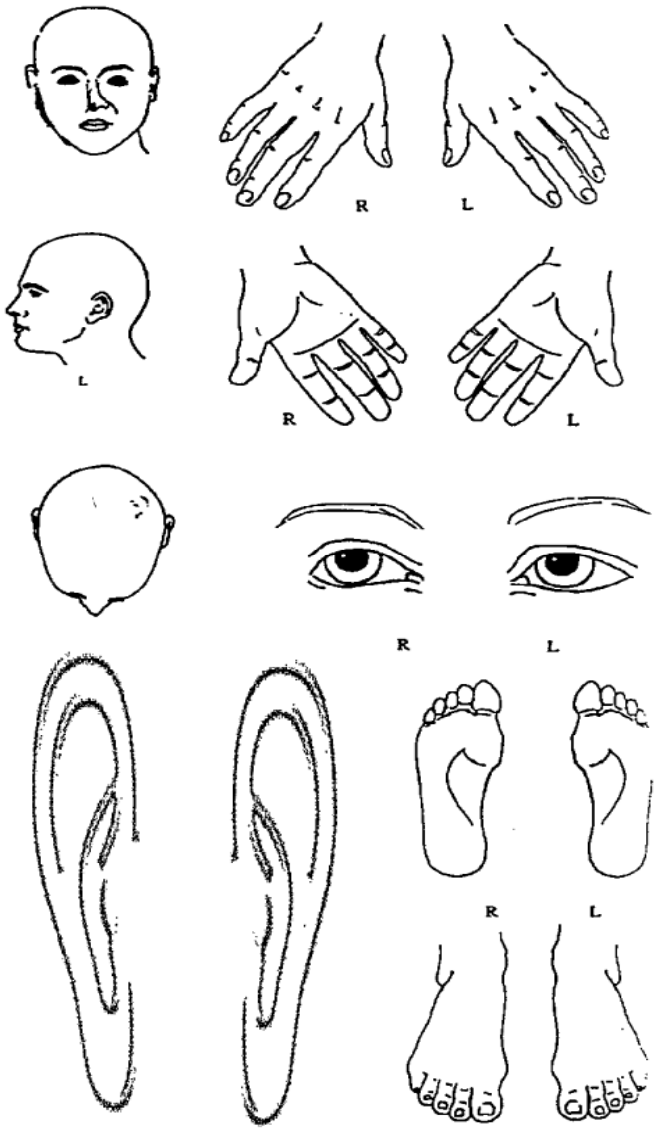
Body-Surface Area Assessment Note

Patient ,
ACCT#
DOB

Print Date
FC SEX Location

MDA #





Area	%BSA for region	% BSA Patch	% BSA Plaque	% BSA Tumor
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper arms	8			
Foreanns	6			
Hands	5			
Thighs	19			
Lower leg	14			
Feet	7			
Total	100			

Total BSA involvement % BSA Patch _____
% BSA Plaque _____
% BSA Tumor _____
Total BSA involvement % BSA = _____

Signature/Credentials/ID#/Date/Time _____

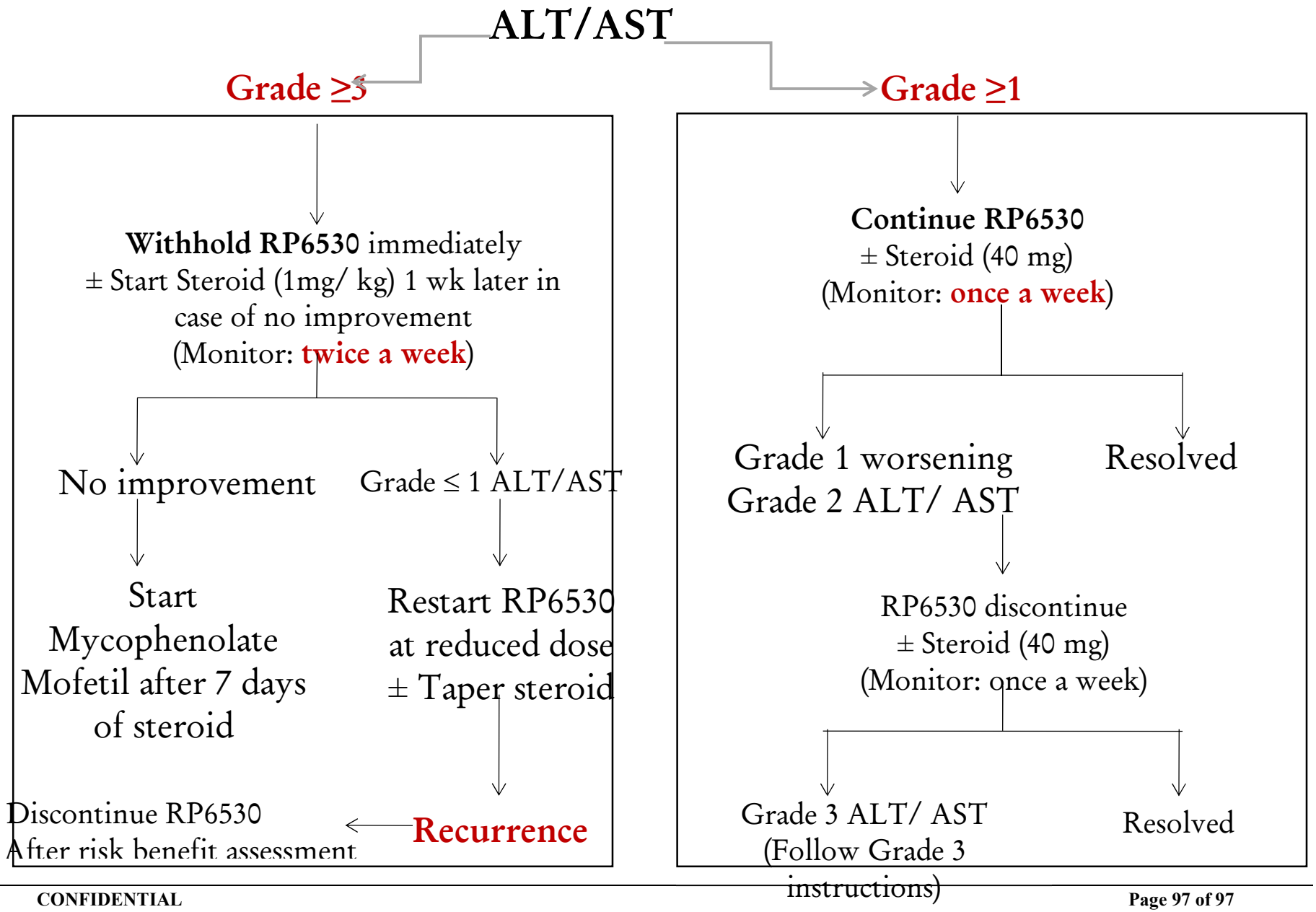
Body Surface Area Assessment Note Page 1 of 1
File Under: Progress Notes

INS999064 12/03 Revised 04/13

Appendix M: Monitoring of Liver enzymes

Grade III elevation of ALT or AST [> 5 X the upper limit of normal (ULN)] have been observed with RP6530 treatment in Dose Escalation Part. Most transaminase elevations were reversible with dose interruption. ***Multiple lines of evidence from literature suggest that this hepatotoxicity was immune mediated. In in view of this, frequent monitoring of liver enzymes is recommended in patient presenting with transaminitis. Steroid can be initiated by the investigator after clinical evaluation of patient.***

- **Grade ≥ 1 Transaminitis:**
  - Maintain RP6530 dose and initiate **prednisone 40 mg daily**.
  - The frequency of monitoring should be weekly in any instance of ALT or AST >3 X ULN (> Grade 1) until resolved.
  - Withhold RP6530 in case of development of grade 2 transaminitis or worsening of Grade 1 transaminitis while on steroids.
- **Grade ≥ 3 Transaminitis:**
  - In of ALT/AST >5–20 X ULN (Grade 3), it is recommended to withhold RP6530 and monitor ALT/AST twice a weekly until levels are Grade ≤1; once this occurs, RP6530 may be resumed at a reduced dose of 400 mg BID.
  - Wait for a week, initiate **prednisone 1 mg/kg** in case no improvement with discontinuation of RP6530 in 1 week.
  - Monitor ALT/AST twice a weekly until levels are Grade ≤1; once this occurs, RP6530 may be resumed at a reduced dose of 400 mg BID and taper steroid.
  - For patients with grade ≥3 transaminitis without immediate response to steroids, mycophenolate mofetil could be considered after 7 days of steroids.
  - If ALT/AST elevation >20 X ULN occurs, RP6530 should be permanently discontinued.
  - In case of recurrence of transaminitis at reduced doses, discontinue RP6530 permanently after assessing risk versus benefit.


ALT/AST
Grade ≥3
Grade ≥1
Withhold RP6530 immediately
± Start Steroid (1mg/ kg) 1 wk later in case of no improvement
(Monitor: twice a week)
No improvement
Grade ≤ 1 ALT/AST
Start Mycophenolate Mofetil after 7 days of steroid
Restart RP6530 at reduced dose
± Taper steroid
Discontinue RP6530
After risk benefit assessment
Recurrence
Continue RP6530
± Steroid (40 mg)
(Monitor: once a week)
Grade 1 worsening
Grade 2 ALT/ AST
Resolved
RP6530 discontinue
± Steroid (40 mg)
(Monitor: once a week)
Grade 3 ALT/ AST
(Follow Grade 3 instructions)
Resolved