CLINICAL TRIAL PROTOCOL

CUDC-907-201

Open-Label, Phase 2 Study to Evaluate the Efficacy and Safety of CUDC-907 in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma, Including Patients With MYC Alterations

Trial Phase	Phase 2
IND Number	115780
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Clinical Trial Protocol Version	Amendment 4 (Version 5.0)
Issue Date	30 August 2016
Original Protocol	18 November 2015

SPONSOR SIGNATURE

Study Title:	Open-Label, Phase 2 Study to Evaluate the Efficacy and Safety of CUDC-907 in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma, Including Patients With MYC Alterations
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Amendment 4:	30 August 2016
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Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, Curis, Inc.:

Amir Hafeez, MD

Senior Medical Director,

Curis, Inc.

Shefali Agarwal (On Behalf of Amir Hafeez)

Signature

09/01/2016

Date

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States federal regulations and International Conference on Harmonisation (ICH) guidelines.

_____ _____

Investigator Signature Date

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Investigator Name

_____

_____

_____

Institution

1. SYNOPSIS

Protocol Title: Open-Label, Phase 2 Study to Evaluate the Efficacy and Safety of CUDC-907 in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma, Including Patients With MYC Alterations
Sponsor Protocol Number: CUDC-907-201
Phase: Phase 2
Sponsor: Curis, Inc.
Name of Investigational Product: CUDC-907
IND Number: 115780
EudraCT Number: 2014-004509-34
Trial Centers/Countries: Up to 65 sites in the United States (U.S.) and ex-U.S.
Planned Trial Period: 2 years
Trial Objectives: Primary Objective: • To evaluate the efficacy of CUDC-907 as measured by the objective response rate (ORR) in subjects with relapsed and/or refractory (RR) diffuse large B-cell lymphoma (DLBCL) with MYC-altered disease. Secondary Objectives: • To evaluate progression-free survival (PFS), median PFS, and PFS at 6 months (PFS6). • To evaluate overall survival (OS). • To evaluate the disease control rate (DCR) and duration of response (DOR). • To evaluate the incidence and severity of adverse events (AEs), serious adverse events (SAEs), and other safety parameters in subjects receiving CUDC-907. • To characterize the pharmacokinetics (PK) of CUDC-907.

Trial Objectives (Continued):

Exploratory Objectives:

- To explore the effects of CUDC-907 on disease-associated biomarkers.
- To explore the relationship between disease-associated biomarkers in plasma and tumor tissue. Among biomarkers of interest, BCL2 and BCL6 protein expression and translocation status in particular will be tested in tumor tissue, where possible.
- To explore biomarkers of response for patient selection.
- To explore the relationship between additional biomarkers and biomarker profiles that may influence biologic and clinical responses to CUDC-907.
- To explore the ORR according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014).

Study Design and Methods:

This is a Phase 2, open-label, multicenter trial designed to evaluate the efficacy and safety of CUDC-907 in subjects 18 years and older with RR MYC-altered DLBCL.

Figure 1 depicts the study design. Patients with RR DLBCL will be eligible for treatment with CUDC-907 as long as they have tumor tissue available that can be tested for MYC-altered disease. This is defined as *MYC* translocation by FISH, or MYC expression in ≥ 40% of tumor cells by IHC staining, and/or *MYC* gene copy number gain by FISH based on central testing of one of the following:

- Fresh tumor tissue obtained from biopsy accessible lesions with low estimated risk for serious complications (less than 2%), or
- Archived tumor tissue (most recent available)

Subjects will be required to submit archival tumor samples (most recent available) or fresh tumor samples for central FISH and IHC testing. Subjects whose tumors have been previously characterized as MYC-altered are strongly encouraged to enter the study. For subjects who enter the study with unconfirmed MYC-altered disease, fresh tumor samples are preferred.

All eligible subjects will receive the following treatment:

- CUDC-907 60 mg (2 × 30 mg capsules) orally (PO) for 5 days on/2 days off (5/2) (21-day cycles).

Based on central testing and review, subjects will be classified into one of the following categories:

(1) Group A: *MYC* translocation^{+} by FISH,

(2) Group B: MYC expression in ≥ 40% of tumor cells by IHC and/or *MYC* gene copy number gain by FISH, or

(3) Group C: *MYC* translocation^{-} by FISH, and MYC expression in < 40% of tumor cells, and no *MYC* gene copy number gain by FISH.

Subjects will be assigned to Groups A, B, or C according to their MYC status as described above. Subjects who are both *MYC* translocation^{+} by FISH and have MYC expression in ≥ 40% of tumor cells by IHC and/or *MYC* gene copy number gain by FISH will be classified as *MYC* translocation^{+} and assigned to Group A.

Enrollment may continue until the minimum number of subjects are enrolled in Groups A and B.

Study Design and Methods (Continued):

Subjects in all groups will continue to receive treatment until they meet criteria for treatment discontinuation. Efficacy evaluations will include restaging assessments, physical examination, review of lymphoma symptoms, survival status, and other procedures, as necessary. Disease response by radiologic imaging will be assessed according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007). The exploratory efficacy endpoint of ORR will be assessed according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014).

Efficacy assessments will be performed using computed tomography/magnetic resonance imaging (CT/MRI) scans of the neck, chest, abdomen, and pelvis.

Skull base-to-mid thigh positron emission tomography (PET) scan is recommended but not mandated.

Contrast-enhanced MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT or if contrast-enhanced CT scanning cannot be performed due to medical condition(s). For each patient, the modality/modalities utilized at screening will be followed throughout the patient's time on study. While additional modalities may be used depending on assessment needs and disease specifics, technologies used at screening will continue to be followed at each restaging assessment to enable direct comparison with the baseline assessment.

Disease response will be assessed both by the local Investigator and the independent review committee.

Safety will be assessed by the incidence and severity of AEs as determined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). Additional safety parameters will include physical examination and vital signs, as well as hematology and serum chemistry laboratory tests.

Planned Number of Subjects: Approximately 200 subjects will be enrolled in the study.

Schedule of Visits and Assessments:

During Treatment:

Subjects will have 4 clinic visits during Cycle 1 (Days 1, 5, 12, and 15) and clinic visits every 3 weeks on Day 1 of every cycle thereafter. For the first 50 subjects enrolled on amendment 4, there will also be a Cycle 1 Day 8 visit. Subjects who continue past Cycle 13 will have clinic visits every 6 weeks on Day 1 of every other cycle (Cycles 14, 16, 18, etc.). Safety assessments will be conducted at each clinic visit.

Subjects will have efficacy assessments (CT/MRI) performed at the end of Cycles 2, 4, and 6 (each ± 3 days). If ^{18}F-fluorodeoxyglucose (FDG)-PET/CT is acquired at baseline, follow-up FDG-PET/CT imaging at Cycle 4 and at Cycle 10 is required. Scans will be sent for a central radiographic review.

Subjects who continue to receive CUDC-907 after Cycle 6 will have disease response assessments (CT/MRI) performed every 12 weeks ± 1 week (i.e., Cycles 10, 14, 18) until Cycle 18 in the first 12 months with scans collected through the first year, then every 24 weeks ± 2 weeks (i.e., Cycles 26, 34) until progressive disease (PD) or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care).

Schedule of Visits and Assessments (Continued):

During Post-Treatment Follow-Up

All subjects will have PFS and survival assessments every 12 weeks during the first 6 months, then every 24 weeks until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care). Overall survival may be checked by phone every 3 months and data entered in the electronic case report form (eCRF).

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Age ≥ 18 years.
2. At least 2 but no more than 4 prior lines of therapy for the treatment of *de novo* DLBCL and ineligible for (or failed) autologous or allogeneic stem cell transplant (SCT) (salvage therapy, conditioning therapy and maintenance with transplant will be considered one prior treatment). **NOTE:** For follicular lymphoma transformed to DLBCL (t-FL/DLBCL), single-agent non-cytotoxic therapy will not be considered as a line of therapy.
3. Histopathologically confirmed diagnosis of one of the following:
   - RR DLBCL per the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors (Swerdlow et al, 2008).
   - High grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 rearrangements, or DLBCL, not otherwise specified (NOS), per the 2016 revision of the WHO classification of lymphoid neoplasms (Swerdlow et al, 2016).
   - Diagnosis of t-FL/DLBCL is allowed. However, other B-cell lymphomas including other transformed indolent lymphomas/DLBCL per the 2008 WHO classification, HGBL, NOS per the 2016 WHO classification, and Burkitt lymphoma are not eligible.
4. Confirmed availability of viable tissue (defined as most recent available archival tumor tissue, or fresh tumor samples) for central laboratory FISH and IHC testing prior to study dosing. For subjects who enter the study with unconfirmed MYC-altered disease, fresh tumor samples are preferred.

   NOTE: To facilitate early testing of MYC status, a separate informed consent form (ICF) specific for MYC testing will be available to be signed prior to sample testing and the signing of the main ICF.
5. CT scan showing at least 1 or more clearly demarcated lymph node(s) with a long axis > 1.5 cm and short axis > 1.0 cm **or** 1 clearly demarcated extranodal lesion(s) with a long axis > 1.0 cm and short axis > 1.0 cm. Baseline FDG-PET scans, if used, must demonstrate positive lesions compatible with CT-defined anatomical tumor sites.

Inclusion and Exclusion Criteria (Continued):

Inclusion Criteria (Continued):

6. Presence of RR disease per Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007).
   - Relapsed disease is defined by DLBCL confirmed by excisional/incisional biopsy (preferred) or fine needle aspiration (FNA) or core needle biopsy (CNB) after a complete response (CR) or unconfirmed complete response (CRu).
     - For relapse during prior treatment, biopsy/FNA reconfirmation of the lymphoma is recommended but not mandatory.
   - Refractory disease is defined by (a) PD during prior treatment, (b) stable disease (SD) after ≥ 3 cycles of prior treatment, or (c) partial response (PR) after ≥ 6 cycles of prior treatment, or for stage II disease, ≥ 3 cycles of treatment and definitive involved field radiotherapy.
     - For sustained PR after prior treatment, confirmation biopsy for DLBCL is preferred. An FNA may be acceptable, but if inappropriate (e.g., due to biopsy inaccessibility), the Sponsor may determine eligibility following review of imaging results and disease history.
     - For SD or PD after prior treatment, reconfirmation of DLBCL by biopsy (preferred) or FNA is recommended but not mandatory.
7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
8. Recovery to Grade 1 or baseline of any toxicity due to prior anticancer therapies (excluding alopecia).
9. Absolute neutrophil count (ANC) ≥ 1,000/μL; platelets ≥ 75,000/μL; creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/minute as determined by Cockcroft-Gault (using actual body weight) or by 24-hour urine collection measurements of creatinine; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 × ULN; total bilirubin ≤ 1.5 × ULN or ≤ 3 ULN for patients with documented Gilbert's syndrome. Platelet transfusions and administration of granulocyte colony-stimulating factors to help patients meet eligibility criteria are not allowed within 1 week prior to screening complete blood count (CBC) or Cycle 1, Day 1 treatment.
10. Women of childbearing potential must have a negative serum or urine pregnancy test (not applicable after bilateral oophorectomy and/or hysterectomy).
11. Men and women of childbearing potential and their partners must agree to use adequate birth control throughout their participation in the study and for 30 days following the last study treatment. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence. Acceptable methods of contraception are described in Table 3.
12. In the Investigator's judgement, able to provide written informed consent and follow protocol requirements.

Inclusion and Exclusion Criteria (Continued):

Exclusion Criteria:

1. Known primary mediastinal, ocular, epidural, testicular or breast DLBCL.
2. Patients must not have active CNS involvement of their malignancy. Patients with prior brain metastases are permitted, but must have completed treatment and have no evidence of active CNS disease (clear cerebrospinal fluid [CSF]) for at least 4 weeks prior to the first dose of CUDC-907. Intrathecal chemoprophylaxis to prevent the emergence or recurrence of lymphoma in the CNS is permitted on study and may be administered per institutional guidelines.
3. Known allergy or hypersensitivity to phosphatidylinositol 3-kinase (PI3K) inhibitors or any component of the formulations used in this study.
4. Cytotoxic anticancer therapy (e.g., alkylating agents, anti-metabolites, purine analogues) within 2 weeks of study entry.
5. Radiotherapy delivered to non-target lesions within one week prior to starting study treatment or delivered to target lesions that will be followed on the study (**NOTE**: prior sites of radiation will be recorded).
6. Treatment with experimental therapy within 5 terminal half-lives ($t_{1/2}$) or 4 weeks prior to enrollment, whichever is longer.
7. Current or planned glucocorticoid therapy, with the following exceptions:
   - Doses ≤ 1 mg/kg/day prednisolone or equivalent glucocorticoid and inhalational therapies for conditions such as mild chronic obstructive pulmonary disease (COPD) and asthma are allowed.
   - Replacement dosing of steroids (defined as < 30 mg/day hydrocortisone or the equivalent) is allowed, provided that the steroid dose has been stable or tapering for at least 14 days prior to the first dose of CUDC-907.
8. Graft versus host disease following transplant within 100 days prior to study treatment.
9. Major surgery, other than diagnostic surgery, occurring 4 weeks prior to study treatment.
10. Diabetes mellitus that is not controlled with medication.
11. Serious infection requiring intravenous antibiotic therapy within 14 days prior to study treatment.
12. Uncontrolled or severe cardiovascular disease, including myocardial infarction, unstable angina, or atrial fibrillation (AFib) within 6 months prior to study treatment, New York Heart Association (NYHA) Class II or greater congestive heart failure, serious arrhythmias requiring medication for treatment, clinically significant pericardial disease, cardiac amyloidosis, or QTc with Fridericia's (QTcF) correction that is unmeasurable or ≥ 480 msec on screening electrocardiogram (ECG). (Note: for QTcF ≥ 480 sec on the screening ECG, the ECG may be repeated twice at least 24 hours apart; the mean QTcF from the three screening ECGs must be < 480 msec in order to meet eligibility for trial participation).

Inclusion and Exclusion Criteria (Continued):

Exclusion Criteria (Continued):

13. Gastrointestinal disease or disorder that could interfere with the swallowing, oral absorption, or tolerance of CUDC-907. This includes uncontrolled diarrhea (> 1 watery stool/day), major abdominal surgery, significant bowel obstruction and/or gastrointestinal diseases that could alter the assessment of PK or safety, including but not limited to: irritable bowel syndrome, ulcerative colitis, Crohn's disease and hemorrhagic coloproctitis.
14. History of other invasive malignancy, unless adequately treated with curative intent and with no known active disease present within 1 year prior to the first dose of study drug, provided it is deemed to be at low risk for recurrence by the treating physician.
    - These conditions include but are not limited to non-melanoma skin cancer, carcinoma *in situ*, (including superficial bladder cancer), cervical intraepithelial neoplasia and organ-confined prostate cancer.
15. Known infection with human immunodeficiency virus (HIV).
16. Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
    - Regardless of hepatitis B surface antigen (HBsAg) status, if hepatitis B core antibody (HBcAb) is positive, then HB DNA testing will be performed and if positive the patient will be excluded.
    - Regardless of hepatitis RNA level, patients who are positive for hepatitis C antibody (anti-HCV) will be permitted to enroll provided that they meet all eligibility criteria and are without evidence of cirrhosis. Patients diagnosed with HCV < 6 months prior to enrollment will be considered to have acute HCV and excluded unless viral load is undetectable.
17. Pregnant or breast-feeding women.
18. Unstable or clinically significant concurrent medical condition that would, in the opinion of the Investigator, jeopardize patient safety and/or compliance with the protocol.

Dose and Mode Of Administration/Dosing Schedule:

Each cycle will consist of 21 days.

- CUDC-907 60 mg (2 × 30 mg capsules) administered PO 5/2.

Planned Duration of Treatment:

CUDC-907 will be taken until disease progression, withdrawal from study, unacceptable toxicity, pregnancy, initiation of another anticancer or experimental therapy, noncompliance with study procedures, or study discontinuation.

Dose and/or schedule intensity of CUDC-907 may be reduced due to toxicity.

Criteria for Evaluation:

Efficacy:

The Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007), will be used to evaluate all subjects on active treatment.

Primary efficacy endpoint: ORR (central determination)

Secondary efficacy endpoints:

- ORR (local determination)
- PFS, median PFS, and PFS6 (central and local determination)
- OS
- DCR and DOR (central and local determination)

Exploratory efficacy endpoint:

- ORR according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014)

Safety:

The incidence and severity of AEs, including treatment-related events, events leading to death, SAEs, and events resulting in study treatment discontinuation.

Pharmacokinetics:

Population PK of CUDC-907 will be evaluated in plasma samples based on prior established parameters.

Biomarkers:

Tumor, blood, and plasma samples will be evaluated in all subjects to identify other markers potentially predictive of response to CUDC-907. Genomic material from tumor, blood and plasma samples will be assessed for aberrations in genes associated with disease and/or treatment targeted pathways. Gene expression profiling will be applied to genomic material isolated from tumor tissue in part to determine cell of origin classification. In addition, protein analysis will be conducted on tumor and plasma samples to evaluate baseline levels and/or changes in biomarkers related to the disease and/or targeted pathways, if feasible. BCL2 and BCL6 protein expression and translocation status are among the disease-related biomarkers that will be tested in tumor tissue, if feasible.

Statistical Considerations:

Efficacy Endpoints:

The primary efficacy endpoint is ORR as determined by the central determination of disease response. Secondary endpoints include ORR as determined by the investigative site, and PFS, median PFS, PFS6, OS, DCR, and DOR as determined by both the central determination of disease response and investigator site. An exploratory efficacy endpoint will assess ORR (CR, PR) according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014).

Statistical Considerations (Continued):

Analysis Populations Evaluable for Safety and Efficacy:

The Intent-to-Treat (ITT) Population will consist of all subjects assigned to Groups A and B. The primary analyses of efficacy will be conducted based on the ITT Population.

The Evaluable Population will consist of all subjects in Groups A and B who receive at least one full cycle of treatment and have at least one post-baseline disease assessment and have not had major protocol deviations that are thought to have materially impacted efficacy outcomes. Major protocol deviations will be identified prior to database lock. Secondary analyses of efficacy will also be conducted based on the Evaluable Population. In addition, the primary efficacy endpoint (ORR) will also be assessed using the Evaluable Population as a secondary analysis.

The Safety Population will consist of all subjects who receive any study treatment. All safety analyses will be conducted based on this population.

Sample Size Determination:

The sample size for Groups A and B was determined based on the following:

With a sample size of 50 subjects in Groups A and B with an ORR of 30.0%, a two-sided 95% confidence interval employing the exact binomial method will extend from 17.9% to 44.6%. This confidence bound (CB) about the observed ORR is thought to adequately characterize the disease response of these populations after receiving CUDC-907.

Interim Analyses:

- Interim analyses of efficacy using the Evaluable Population will be performed after ORR has been determined in 25 evaluable subjects for both Groups A and B, separately. In both Groups A and B, the ORR using the local determination of disease response will be obtained. If the lower bound of a single-sided 95% confidence interval using the exact binomial method is less than 10% (i.e., 5 responses or less out of 25 patients) in either group, enrollment in that group will not continue.

Efficacy Analyses:

The primary analyses of efficacy will be conducted based on the ITT Population and the interim analyses will be performed on the Evaluable Population. However, secondary analyses will be performed on the ITT and Evaluable Populations. The primary efficacy endpoint, ORR, will be based on the proportion of subjects with CR or PR using the central determination of disease response in both Groups A and B, separately. The estimate will be accompanied by a two-sided exact binomial 95% CB.

Progression-free survival, OS, and DOR will be summarized descriptively using the Kaplan-Meier method.

Progression-free survival, median PFS, and PFS6 based on the Kaplan-Meier analyses will be reported. For OS, the estimated rates at 3, 6, 9 and 12 months based on the Kaplan-Meier analyses will be reported. For duration of objective response, the estimate of the median based on the Kaplan-Meier analyses will be reported. Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of the product diameters in measurable nodes and nodal masses. Secondary analyses of efficacy will be conducted based on the Evaluable Population. The estimate will be accompanied by a two-sided exact binomial 95% lower CB.

Statistical Considerations (Continued):

Safety Analyses:

The analyses of safety will be conducted based on the Safety Population. Safety will be assessed based on AEs, SAEs, laboratory values, vital signs, and ECG results. Summary tables will be produced for all reported treatment-emergent adverse events (TEAEs) (AEs that start or worsen on or after the first administration of study treatment) tabulated by the current version of the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tabular summaries will be provided for: all TEAEs, TEAEs by relationship to study treatment, TEAEs by severity, TEAEs occasioning treatment modification, and serious TEAEs.

Hematology and serum chemistries will be summarized using conventional summary statistics (mean, standard deviation, median, and range) for the following: baseline value, minimum and maximum post-baseline values, average post-baseline value, and last post-baseline value. Standard shift tables will also be prepared presenting worst post-baseline toxicity grade vs. baseline. Vital signs and ECG results will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range by time point in the same manner described for laboratory values.

Pharmacokinetic Analyses:

Population PK analysis will be conducted to further understand the PK profile of CUDC-907 in patients with RR MYC-altered DLBCL. Preliminary PK information has been collected during Phase 1, and the basic PK models of the drug have been established. In this study, blood samples will be obtained at 2 hours post-dose on Cycle 1 Day 1, Cycle 4 Day 1, and on Day 1 of every other cycle thereafter (i.e., Day 1 of Cycles 6, 8, 10 etc.). In addition, for the first 50 subjects enrolled on amendment 4, blood samples will also be obtained 2 hours post-dose on Days 8 and 15 of Cycle 1.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Abbreviations

Abbreviation	Definition
5/2	Five days on/two days off
ABC	Activated B-cell-like
AE	Adverse event
AFib	Atrial fibrillation
AKT	Protein kinase B
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BIW	Twice weekly
BUN	Blood urea nitrogen
CB	Confidence bound
CBC	Complete blood count
cfDNA	Cell-free DNA
CFR	Code of Federal Regulations
CNB	Core needle biopsy
CNS	Central nervous system
COO	Cell of origin
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRu	Unconfirmed complete response
CSF	Cerebrospinal fluid
CT	Computed tomography
DCR	Disease control rate
DE	Double expressor
DH	Double hit
DHAP	Dexamethasone, cytarabine, and cisplatin
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity

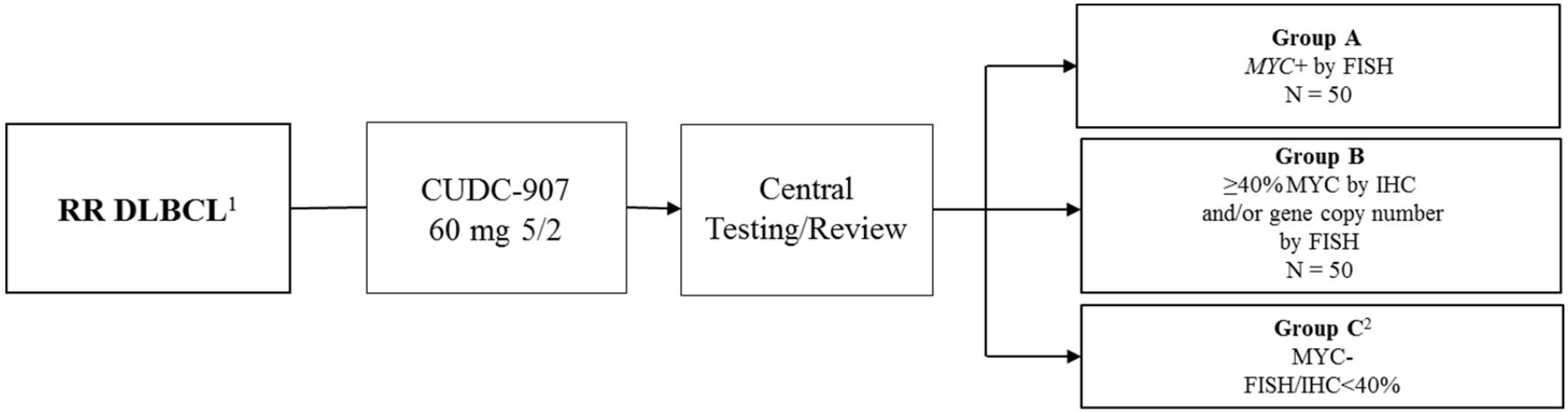
Abbreviation	Definition
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event free survival
EOT	End of Therapy
FDA	Food and Drug Administration
FDG	^{18}F-fluorodeoxyglucose
FIH	First-in-human
FISH	Fluorescence *in-situ* hybridization
FL	Follicular lymphoma
FNA	Fine needle aspiration
GCB	Germinal center B-cell
GCP	Good Clinical Practice
GEP	Gene expression profiling
GMP	Good manufacturing practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDAC	Histone deacetylase
HGBL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug Application
IPI	International Prognostic Index
IRB	Institutional Review Board

Abbreviation	Definition
ITT	Intent-to-Treat
IV	Intravenous
JAK	Janus kinase
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
mCR	Metabolic complete response
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
NYHA	New York Heart Association
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PI	Principal Investigator
PK	Pharmacokinetic
PO	*Per os* (orally)
PR	Partial response
PTEN	Phosphatase and tensin
QTcF	QTc with Fridericia's
QD	Once daily
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RP2D	Recommended Phase 2 dose
RR	Relapsed and/or refractory
SAE	Serious adverse event
SCT	Stem cell transplant

Abbreviation	Definition
SD	Stable disease
SRC	Safety Review Committee
STAT	Signal transducer and activator of transcription
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse events
t-FL/DLBCL	Transformed follicular lymphoma subtype of diffuse large B-cell lymphoma
TH	Triple hit
TIW	Thrice weekly
ULN	Upper limit of normal
U.S.	United States
WBC	White blood cell

4. STUDY SCHEMATIC

Figure 1: Study Design



DLBCL = diffuse large B-cell lymphoma; RR = relapsed and/or refractory

[1] Subjects with RR DLBCL who have had at least 2 but no more than 4 prior lines of therapy for DLBCL will receive CUDC-907. Tumor samples from all subjects will be tested centrally to obtain full tumor MYC profile. Upon central review of MYC status, subjects will be assigned to Groups A, B or C. Subjects who qualify for both Groups A and B will be classified as *MYC* translocation^{+} and assigned to Group A.

[2] Subjects who do not meet criteria for Groups A or B based on central laboratory testing and review will be assigned to Group C.

5. SCHEDULE OF EVENTS

5.1. Schedule of Events

Assessments	Screening		Treatment Period (21-Day Cycles)[1]								Post-Treatment	
	Days -28 to -1	Days -7 to -1	Cycle 1					Cycle 2-6	Cycle 7+	EOT	F/U ≤ 6 months	F/U > 6 months
			Day 1[2]	Day 5	Day 8	Day 12	Day 15	Day 1[2]	Day 1[2]	D30 ± 7d post last dose	q12 weeks ± 1 week	q24 weeks ± 2 weeks
Informed consent	X											
Inclusion/exclusion	X											
Medical and medication history/demographics	X											
Archival/fresh tumor tissue[3,21,22]	X											
Physical examination[2]		X	X					X	X	X		
Symptom-directed physical examination				X		X					X[4]	X[4]
ECOG performance status		X	X					X	X	X		
IPI score	X										X	X
Height		X										
Vital signs[5]		X	X	X		X		X	X	X		
ECG		X								X		
Pregnancy test[6]		X	X					X	X	X		
Lymphoma assessment[7]			X					X	X	X[8]	X[4]	X[4]
Radiologic assessment[18] (CT/MRI)	X[19]							X[9]	X[9]	X[8]	X[4]	X[4]
Radiologic assessment[18] (FDG-PET/CT)	X[20]							X[10]	X[10]	X[8]	X[4]	X[4]
Survival status[11]											X	X
CBC w/diff		X	X	X		X		X	X	X		
Chemistries[12]		X	X	X		X		X	X	X		
Urinalysis	X											
Plasma for biomarker sampling	X							X	X			
Plasma for PK sampling[13]			X		X[23]		X[23]	X	X			

Tissue for biomarker sampling[14]	X						X					
Pharmacogenomic sampling	X											
Concomitant medications	X	X	X	X			X	X	X	X	X[15]	X[15]
Adverse events			X	X			X	X	X	X	X[16]	X[16]
CUDC-907 dosing			5 days on/2 days off[17]									

Definitions: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CT = computed tomography; d = day (s); diff = differential; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = End of Therapy; FISH = fluorescence *in-situ* hybridization; FDG-PET = ^{18}F-fluorodeoxyglucose-positron emission tomography; F/U = follow-up; ICF = informed consent form; IHC = immunohistochemistry; IPI = International Prognostic Index; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetic; q12 = every 12; q24 = every 24; SAEs = serious adverse events
Footnotes:

1. The window for all treatment assessments/procedures is ± 2 days. If extenuating circumstances prevent a subject from starting or completing treatment, or a scheduled procedure or assessment within the protocol-specified time, the subject may continue to be treated on the study only with permission of the Curis Medical Monitor or designee clinician.
2. Physical exam, performance status, weight, CBC w/differentials and serum chemistry labs may be performed up to 3 days prior to Day 1 of each cycle. Subjects who continue past Cycle 13 will only be required to have a Day 1 visit at the beginning of every other cycle (14, 16, 18, etc.). The Cycle 1, Day 1 physical examination is not required if the screening physical examination was conducted within 3 days prior to administration of the first dose of study drug (Cycle 1, Day 1).
3. Subjects will be required to submit archival tissue samples (most recent available) or fresh tumor samples for central FISH and IHC testing. For subjects with unconfirmed MYC-altered disease, fresh tumor samples (obtained from biopsy-accessible lesions with less than 2% estimated risk for serious complications) are preferred.
4. Performed until time of disease progression, withdrawal of consent, or any other criteria that would make the subject unable to be followed for disease response.
5. Vital signs include blood pressure, heart rate, respiratory rate, temperature, and weight.
6. A serum or urine pregnancy test will be performed for women of childbearing potential at least once per cycle prior to dosing, or more frequently as clinically indicated, as well as during Screening and at the EOT visit.
7. Lymphoma assessment consists of physical examination, a review of the subject's current signs and symptoms, B symptoms, and concomitant medications.
8. Lymphoma and radiologic assessments to be done only if not performed within 4 weeks of the EOT visit.
9. Up to Cycle 6, radiologic assessments using CT/MRI scans of the neck, chest, abdomen, and pelvis are required during the last week (Day 15 -21) of Cycle 2, Cycle 4, and Cycle 6 (each ± 3 days). After Cycle 6, radiologic assessments (CT/MRI) are required every 12 weeks (± 1 week) (i.e., Cycles 10, 14, 18) until Cycle 18, and then every 24 weeks ± 2 weeks (i.e., Cycles 26, 34) until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care). Contrast-enhanced MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT or if contrast-enhanced CT scanning cannot be performed due to medical condition(s). For each subject, the modality/modalities utilized at screening will be followed throughout the subject's time on study.

10. Skull base-to-mid thigh PET scan is recommended but not mandated. If FDG-PET/CT is acquired at baseline, follow-up FDG-PET imaging at Cycle 4 and at Cycle 10 is required. 5-PS score of 1 and 2 are considered PET-negative; 5-PS score of 3, 4, or 5 are considered PET-positive.
11. All subjects will have PFS and survival assessments every 12 weeks during the first 6 months, then every 24 weeks until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care). Overall survival may be checked by phone every 3 months and data entered in the eCRF.
12. Sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose.
13. Plasma for PK sampling will be drawn at 2 hours post-dose on Cycle 1 Day 1, Cycle 4 Day 1, and on Day 1 of every other cycle thereafter (i.e., Day 1 of Cycles 6, 8, 10, etc.) for all subjects.
14. Optional tumor biopsies (from subjects with accessible tumor lesion) for biomarker sampling should be obtained any time during screening up to pre-dose Cycle 1, Day 1 and within 8 hours post-dose on any dosing day from Cycle 1, Day 15 through Cycle 2, Day 1.
15. Anti-cancer therapies only.
16. Adverse events will be collected until 30 days post the last dose of study treatment. After the post 30-day time point, only treatment-related SAEs will be captured.
17. CUDC-907 will be administered in the clinic on all PK and tissue sampling days.
18. Disease response by radiologic imaging will be assessed according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007). The exploratory efficacy endpoint of ORR will be assessed according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014). Assessments are performed both by the local Investigator and by the independent review committee.
19. CT scan showing at least 1 or more clearly demarcated lymph node(s) with a long axis > 1.5 cm and short axis > 1.0 cm OR 1 clearly demarcated extra nodal lesion(s) with a long axis > 1.0 cm and short axis > 1.0 cm. Every effort should be made to use the same imaging facility and scanner for each scan throughout the study to ensure reproducibility of measurements.
20. Baseline FDG-PET scans, if used, must demonstrate positive lesions compatible with CT-defined anatomical tumor sites.
21. To facilitate early testing of MYC status, and depending on local site requirements, a separate ICF specific for MYC testing will be available to be signed prior to sample testing and the signing of the main ICF. All other study tests and procedures must be done during the Screening period (Day -28 to Day -1).
22. Local MYC results performed previously should be entered into the eCRF at screening although central testing is required for all patients.
23. For the first 50 subjects enrolled on amendment 4, 2 additional blood draws will be required 2 hours post-dose on Days 8 and 15 of Cycle 1.

6. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

CUDC-907 is a first-in-class, rationally-designed small molecule that dually inhibits histone deacetylase (HDAC) (class I and II) and phosphatidylinositol 3-kinase (PI3K) (class I α, β, and δ) enzymes (Qian et al, 2012). This unique combination suppresses multiple signaling pathways critical for cell proliferation, survival, and migration by targeting oncogenic gene expression and protein activities critical for cancer growth and potentially mitigating the emergence of acquired drug resistance. CUDC-907 has been shown to inhibit activation of PI3K/protein kinase B (AKT), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), and mitogen-activated protein kinase (MAPK) signaling pathways in both solid tumor and hematologic cancer cell lines. The anti-tumor growth and pro-apoptotic activity of CUDC-907 has also been shown to be more potent than single-target HDAC or PI3K inhibitors, as demonstrated in a variety of cultured and implanted cancer cell lines representing B- and T-cell lymphomas, as well as other hematologic malignancies.

6.1.1. Relapsed/Refractory MYC-Altered Diffuse Large B-Cell Lymphoma

6.1.1.1. Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL), a biologically aggressive type of non-Hodgkin lymphoma (NHL) that arises from B cells, is the most common form of NHL in the United States (U.S.) and Europe. DLBCL meets requirements for orphan disease status in the U.S. and Europe, with a prevalence of less than 200,000 persons in the U.S. and fewer than 5 persons per 10,000, respectively (Howlader et al, 2014; Bray et al, 2013). The U.S. Food and Drug Administration (FDA) granted CUDC-907 orphan drug status for this disease on April 2, 2015.

DLBCL is a heterogeneous disease. While subtypes differ in prognosis and response to treatment, the disease is rapidly fatal if untreated. Clinically, patients with DLBCL usually present with advanced and often extranodal disease. DLBCL can be primary (arising *de novo*) or secondary (representing progression or transformation of a less aggressive lymphoma, such as follicular lymphoma). Since approval of rituximab for the treatment of DLBCL, this agent has become an integral part of various cytotoxic standards of care, including R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). While R-CHOP is commonly used in 1st line treatment, a considerable proportion of patients with advanced stage disease and certain adverse clinical risk factors are not cured with this or other standard therapies (Friedberg and Fisher, 2008). Approximately 40% of patients have refractory disease or disease that relapses after initial response and most patients with relapsed DLBCL ultimately succumb to the disease (Sehn, 2012). Based on systematic review of the literature focused on interventions for relapsed and/or refractory (RR) DLBCL, median progression-free survival (PFS) ranges from 1 - 10 months and median overall survival (OS) ranges from 4 to 13 months (Colosia et al, 2014).

The prognosis for subjects with DLBCL has long been considered to be dependent on risk factors such as those measured by the International Prognostic Index (IPI). The IPI assigns patients to 1 of 4 risk category groups on the basis of 4 factors (i.e., age > 60, stage III or IV

disease, elevated lactate dehydrogenase (LDH), and more than 1 extranodal site of disease) that correlate with 5 year OS ranging from 23% to 75% (Gandhi, 2014). Since the IPI does not provide information to guide the choice of therapy, additional risk biomarkers – particularly those that might serve as targets for effective interventions – might better characterize subjects' lymphoma subtypes and the interventions most likely to benefit them.

Gene expression profiling (GEP) studies enable consideration of the molecular subtype of DLBCL and provide opportunities to identify subjects with particularly aggressive lymphomas that might benefit from a novel therapeutic agent. Such studies have shown that DLBCL could be segregated into 2 distinct subgroups based on cell of origin (COO) referred to as germinal center B-cell (GCB) and the activated B-cell-like (ABC) subtypes. The ABC DLBCL subtype has been associated with a more aggressive course and poorer prognosis (Carbone et al, 2014) as well as lower likelihood of response to R-CHOP used in the setting of *de novo* disease (Scott et al, 2015). Subjects with RR DLBCL of ABC subtype were also less likely to respond to a commonly used salvage regimen, R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin (Thieblemont et al, 2011).

It has become apparent that the COO paradigm only accounts for a portion of the clinical picture in regards to prognosis for DLBCL subjects. The adverse prognostic impact of rearrangement of the *MYC* oncogene has been well documented for over a decade, both pre- and post- the advent of rituximab (Savage et al, 2009). More recently, overexpression of the MYC protein has also been associated with inferior survival (Horn et al, 2013).

As will be discussed, subjects with MYC-altered DLBCL have much shorter survival (median OS of < 2 years) than subjects without MYC alterations, and the survival for subjects with RR MYC-altered DLBCL is usually measured in months. For these subjects, there is no evidence-based standard of care. Novel therapeutic approaches are needed, rather than simply intensifying cytotoxic therapy.

6.1.1.2. *MYC* Rearrangement in DLBCL

The significance of MYC in DLBCL has been well studied and the preponderance of studies (all retrospective) has shown that MYC-altered disease, defined as *MYC* translocation by fluorescence *in-situ* hybridization (FISH) and/or MYC protein overexpression by immunohistochemical (IHC) staining, and/or gene copy number gain by FISH, independently confers a negative prognosis as reflected by PFS and OS. In a meta-analysis of 24 studies, 18 studies showed that the presence of MYC aberrations was associated with shorter survival in DLBCL (Zhou et al, 2014).

The detection rate for *MYC* rearrangement varies from 5% to 17% of *de novo* DLBCL cases evaluated (note: some studies have distinguished rearrangement of *MYC* alone from double hit [DH]/triple hit [TH] status) (Zhou et al, 2014). A higher proportion of *MYC* rearrangements (up to 69%) are of the GCB (as opposed to ABC) subtype (Tzankov et al, 2014; Gupta et al, 2012; Zhou et al, 2014). Cases with *MYC* translocation usually, but not invariably, show MYC protein overexpression (Kluk et al, 2012; Tzankov et al, 2014; Horn et al, 2013; Valera et al, 2013).

There is evidence that *MYC*-only rearrangement is independently predictive of poor prognosis (Barrans et al, 2010; Klapper et al, 2008; Savage et al, 2009; Akyurek et al, 2012; Valera et al, 2013), particularly when the tumor also overexpresses the MYC protein (Tzankov et al, 2014;

Kluk et al, 2012) and when the tumor is of the GCB subtype (Akyurek et al, 2012; Visco et al, 2013). These data suggest that FISH testing for *MYC* rearrangement should be performed for all patients with DLBCL (Savage et al, 2009). Patients with *MYC* rearrangements in *de novo* DLBCL have been shown to have shorter OS as compared to those with *MYC*-negative *de novo* DLBCL (median OS: 7 vs 16 months). Despite standard therapies, outcomes are similarly poor in patients with *MYC* alone as well as those DH disease defined by concurrent rearrangements of *MYC/BCL2* or *MYC/BCL6* (Macpherson et al, 1999; Li et al, 2016).

This discussion has thus far centered on the implications of MYC-altered status for patients with *de novo* DLBCL. In the setting of RR DLBCL in general, there are diminishing prospects for disease control (median OS of 4 to 13 months). The prognosis for patients with RR MYC-altered DLBCL is even more discouraging. The outcome of patients with DH disease who don't respond to induction or progress after initial response is very poor, with reported 12-month post-progression survival of 20% (Oki et al, 2014), and median post-progression OS of 17 months following salvage therapy (Petrich et al, 2014). Retrospective analysis of the CORAL trial (Gisselbrecht et al, 2011) was performed to identify the prognostic significance of MYC aberrations in patients with RR DLBCL treated with chemotherapy followed by autologous stem cell transplantation (SCT). Four-year OS was 29% in 27 patients who were *MYC*+ versus 62% for those with no MYC aberration (21 of these cases were also identified as DH) (Cuccuini et al, 2012).

Analysis of outcomes makes it clear that traditional approaches to relapsed DLBCL are not effective in MYC-altered DLBCL. It is recommended that patients with MYC-altered B-cell lymphomas in need of further therapy be enrolled into prospective investigational protocols evaluating novel agents with either sound preclinical rationale or demonstrated activity in MYC-driven lymphomas (Cheah et al, 2015).

6.1.1.3. MYC Protein Expression in DLBCL

Recent advances in IHC, notably the commercial development of an anti-MYC antibody, allow quick and accurate detection of MYC protein levels. MYC and BCL2 expression levels are now recognized to represent a more direct measure of the activity of the genes involved, and overexpression of these proteins has been shown to independently confer a very negative prognosis.

Overexpression of MYC protein occurs in approximately one-third of DLBCL cases, of which one-third can be explained by a *MYC* translocation (Johnson et al, 2012). It is expressed in both GCB and ABC subtypes, suggesting a biologic pathway independent of COO. Results of a meta-analysis suggest that both event-free survival (EFS) and OS are inferior in DLBCL with MYC overexpression (Zhou et al, 2014; Gupta et al, 2012; Kluk et al, 2012; Perry et al, 2014; Johnson et al, 2012).

It is even clearer that concurrent overexpression of MYC and BLCL2 is an indicator of poor prognosis. Co-expression of MYC and BCL2 proteins is more common in DLBCL cases of the ABC subtype (> 40%) than with the GCB subtype (< 20%), has an adverse impact on survival and may be a driver of the generally inferior prognosis for patients with the ABC subtype (Hu et al, 2013). Concurrent MYC/BCL2 expression is associated with a lower complete response (CR) rate, shorter OS, and shorter PFS (Green et al, 2012). Median PFS for patients with

MYC/BCL2 expression was reported as 8 months, and median OS ranged from 12 to 18 months (Green et al, 2012; Oki et al, 2014).

Dual positivity for MYC/BCL2 protein in IHC among RR aggressive B-cell lymphomas was more common than in the frontline (Miura et al, 2015). In a study of patients with RR DLBCL, high grade follicular lymphoma (FL), or t-FL/DLBCL, 17/38 patients (45%) overexpressed both MYC and BCL2 proteins. These patients had a lower response rate and shorter median PFS and OS, and fewer opportunities to receive consolidative therapies (HDT or SCT) following achievement of remission (Miura et al, 2015).

6.1.2. Rationale for Development of CUDC-907 for the Treatment of MYC-Altered DLBCL

MYC family genes are among the most frequently deregulated oncogenic drivers in human cancers. MYC genes encode non-catalytic transcriptional regulators that have thus far proven undruggable; therefore, targeting upstream MYC regulators may be an effective strategy to suppress MYC and treat MYC-addicted tumors.

Pharmacologic inhibition of HDAC activity and blockade of the PI3K pathway have both been shown to suppress MYC-induced oncogenic transcriptional programs. HDAC activity is critical for MYC gene regulation, as MYC represses the transcription of a subset of its target genes through the recruitment of HDACs (Kurland et al, 2008; Zhang et al, 2012). HDAC inhibitors restore the expression of genes coordinately suppressed by MYC family members and HDACs and induce rapid and sustained downregulation of expression of MYC itself (Kurland et al, 2008; Zhang et al, 2012; Polack et al, 1987; Chambers et al, 2003; Gui et al, 2004; Liu et al, 2007). HDAC inhibitors also downregulate expression of other oncogenes that cooperate with MYC to induce tumorigenesis, such as BCL2 (Duan et al, 2005). The PI3K pathway plays a central role in regulating MYC homologs at the post-transcriptional level. Activation of PI3K signaling either through mutational activation of PI3K or through loss of the phosphatase and tensin (PTEN) tumor suppressor leads to activation of the effector kinase AKT, which in turns phosphorylates and inhibits GSK3β (Cross et al, 1995). As GSK3β normally phosphorylates MYC and its homologs, which facilitates their recognition by E3 ubiquitin ligases and subsequent ubiquitination and proteasomal degradation, activation of PI3K signaling leads to increased MYC family protein stability, whereas PI3K inhibitors decrease MYC family protein stability (Kenney et al, 2004; Asano et al, 2004; Kumar et al, 2006; Bechard and Dalton, 2009). A recent study showing that PTEN-deficient DLBCL cell lines are addicted to MYC signaling and hypersensitive to PI3K inhibition (Pfeifer et al, 2013) provides evidence that MYC-driven cancers may be particularly sensitive to PI3K inhibition.

As HDACs and PI3K regulate MYC expression through non-overlapping mechanisms, simultaneous HDAC and PI3K inhibition may lead to enhanced MYC suppression.

CUDC-907 is an orally bioavailable small-molecule dual HDAC and PI3K inhibitor that primarily inhibits class I and IIB HDACs and the PI3Kα, β, and δ isoforms (Qian et al, 2012). CUDC-907 shows greater *in vitro* and *in vivo* antitumor activity than single-target HDAC or PI3K inhibitors (Qian et al, 2012), especially in MYC-altered DLBCL models. In preliminary preclinical testing of CUDC-907 in MYC-dependent DLBCL and NUT midline carcinoma cell lines, CUDC-907 treatment leads to a dose-dependent decrease in MYC protein expression, as

well as the inhibition of other critical oncogenic pathways such as the MAPK and STAT pathways. CUDC-907 is also a more potent inhibitor of MYC expression in these cell lines than the HDAC inhibitor, panobinostat (LBH-589), and the pan-PI3K inhibitor, pictilisib (GDC-0941), either alone or in combination. These findings raise the possibility that cancers driven by aberrant overexpression of MYC family genes would be more responsive to simultaneous HDAC and PI3K inhibition with CUDC-907 than single-target therapies.

6.1.3. Clinical Rationale for CUDC-907 Use in RR MYC-Altered DLBCL

The utility of HDAC and PI3K inhibitors for the treatment of hematological malignancies has been recognized by the U.S. FDA, which has approved 4 HDAC inhibitors and 1 PI3K inhibitor for various hematological cancer indications.

The therapeutic potential of CUDC-907 is shown by safety and efficacy data from the completed dose escalation and ongoing expansion stages of ongoing study CUDC-907-101, the first-in-human (FIH) trial. CUDC-907-101 is a Phase 1, open-label, multicenter, dose-escalation trial to evaluate the safety and tolerability of CUDC-907 as a single agent administered orally to subjects with RR lymphoma or multiple myeloma (MM). In the completed dose-escalation phase of CUDC-907-101, subjects received CUDC-907 capsules orally, within 30 minutes of meals, in 21-day cycles according to one of three dosing schedules: once daily (QD), intermittent twice (BIW) or thrice weekly (TIW), and five days on/two days off (5/2). Objective responses, in some cases of extended duration, were achieved with CUDC-907 monotherapy on all schedules tested. On the basis of improved tolerability and comparable efficacy, CUDC-907 administered at 60 mg on the 5/2 schedule was determined to be the recommended Phase 2 dose (RP2D).

CUDC-907 monotherapy has demonstrated a manageable side effect profile and achieved objective responses (ORs) as well as sustained disease control, particularly in the setting of RR DLBCL. The most common treatment-related AEs of any grade have been diarrhea, fatigue, thrombocytopenia, and nausea. No dose-limiting toxicities (DLTs) were observed on the 60 mg 5/2 schedule.

As of the 15 March 2016 data cut-off, among 21 response-evaluable subjects with RR DLBCL receiving CUDC-907 monotherapy at the 60 mg 5/2 schedule (n = 18), or in combination with rituximab (n = 3), 9 (43%) achieved objective responses (3 CRs and 6 partial responses [PRs]); lasting a median of 2.6 months (range: < 1-14+). Among the 5 response-evaluable subjects with MYC-altered DLBCL, 4 (80%) achieved objective responses (3 CRs and 1 PR). Three of these response-evaluable subjects were found to overexpress MYC (≥ 40%) and BCL2 (≥ 70%) by IHC, meeting criteria applied to "double-expressor" (DE) DLBCL. Two of the DE subjects attained objective responses: 1 CR (followed by autologous stem cell transplant) and 1 PR (lasting 4 months). The third subject has experienced lengthy disease stabilization (5.7+ months). All 3 CRs observed on this study occurred in subjects with *MYC* gene copy number gain, including the subject who also had DE DLBCL. Durable clinical benefit in subjects with RR MYC-altered DLBCL in FIH testing further supports this Phase 2 study of CUDC-907.

6.2. Justification of Study Design Considerations

The following is a brief summary of key study design considerations:

- Study subjects will be ≥ 18 years of age with histopathologically confirmed diagnosis of RR DLBCL (including t-FL/DLBCL) who have received at least 2 but no more than 4 prior lines of treatment for DLBCL , and ineligible for (or failed) autologous or allogeneic SCT.
- Subjects will receive CUDC-907 60 mg administered orally on a 5/2 schedule until progression of disease or other criteria for discontinuation of treatment. Each cycle will consist of 21 days.

6.3. Potential Risk and Benefits

Based on available preclinical and clinical safety and response data emerging from the ongoing CUDC-907-101 and CUDC-907-102 trials, ongoing clinical testing of CUDC-907 is considered justified using the dose and dosage regimen preliminarily shown to be reasonably safe and tolerable (Sections 6.1.2, **Error! Reference source not found.** and 6.1.3).

6.3.1. Potential Risks

In CUDC-907-101, low grade (Grade 1 and 2) diarrhea, fatigue, and nausea were the most common drug-related adverse events (AEs) reported in the study. A total of 4 DLTs consisting of diarrhea and hyperglycemia occurred in 3 subjects treated at the highest doses on the QD (60 mg) and intermittent schedules (150 mg BIW and 150 mg TIW). Other drug-related Grade 3 or 4 AEs reported in 2 or more subjects included thrombocytopenia and neutropenia (hematologic AEs) as well as diarrhea, hyperglycemia, and fatigue (non-hematologic AEs). As a result, stringent monitoring of blood counts will be performed.

The planned CUDC-907 dose level, 60 mg 5/2, was reasonably tolerated in the dose-escalation phase of CUDC-907-101 and is currently undergoing further examination in the expansion phase of the trial in subjects with RR DLBCL.

6.3.2. Potential Benefits

Preliminary antitumor efficacy data from CUDC-907-101 evaluating CUDC-907 as monotherapy in subjects with RR DLBCL, including subjects with DE disease, have been promising.

6.4. Good Clinical Practice Statement

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation, Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and Curis policies.

7. TRIAL OBJECTIVES

7.1. Primary Objective

- To evaluate the efficacy of CUDC-907 as measured by the objective response rate (ORR) in subjects with RR DLBCL with MYC-altered disease.

7.2. Secondary Objectives

- To evaluate PFS, median PFS, and PFS at 6 months (PFS6).
- To evaluate OS.
- To evaluate the disease control rate (DCR) and duration of response (DOR).
- To evaluate the incidence and severity of AEs, serious adverse events (SAEs), and other safety parameters in subjects receiving CUDC-907.
- To characterize the pharmacokinetics (PK) of CUDC-907.

7.3. Exploratory Objectives

- To explore the effects of CUDC-907 on disease-associated biomarkers.
- To explore the relationship between disease-associated biomarkers in plasma and tumor tissue. Among biomarkers of interest, BCL2 and BCL6 protein expression and translocation status in particular will be tested in tumor tissue, where possible.
- To explore biomarkers of response for patient selection.
- To explore the relationship between additional biomarkers and biomarker profiles that may influence biologic and clinical responses to CUDC-907.
- To explore the ORR according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014).

8. STUDY DESIGN

8.1. Overall Study Design

This is a Phase 2, open-label, multicenter trial designed to evaluate the efficacy and safety of CUDC-907 in subjects 18 years and older with RR MYC-altered DLBCL.

Figure 1 depicts the study design. Patients with RR DLBCL will be eligible for treatment with CUDC-907 as long as they have tumor tissue available that can be tested for MYC-altered disease. This is defined as *MYC* translocation by FISH, or MYC expression in ≥ 40% of tumor cells by IHC staining, and/or *MYC* gene copy number gain by FISH based on central testing of one of the following:

- Fresh tumor tissue obtained from biopsy accessible lesions with low estimated risk for serious complications (less than 2%), or
- Archived tumor tissue (most recent available)

Subjects will be required to submit archival tumor samples (most recent available) or fresh tumor samples for central FISH and IHC testing. Subjects whose tumors have been previously characterized as MYC-altered are strongly encouraged to enter the study. For subjects who enter the study with unconfirmed MYC-altered disease, fresh tumor samples are preferred.

All eligible subjects will receive the following treatment:

- CUDC-907 60 mg (2 × 30 mg capsules) orally (PO) for 5 days on/2 days off (5/2) (21-day cycles).

Based on central testing and review, subjects will be classified into one of the following categories:

(1) Group A: *MYC* translocation^{+} by FISH,

(2) Group B: MYC expression in ≥ 40% of tumor cells by IHC and/or *MYC* gene copy number gain by FISH, or

(3) Group C: *MYC* translocation^{-} by FISH, and MYC expression in < 40% of tumor cells, and no *MYC* gene copy number gain by FISH.

Subjects will be assigned to Groups A, B, or C according to their MYC status as described above. Subjects who are both *MYC* translocation^{+} by FISH and have MYC expression in ≥ 40% of tumor cells by IHC and/or *MYC* gene copy number gain by FISH will be classified as *MYC* translocation^{+} and assigned to Group A. Enrollment may continue until the minimum number of subjects are enrolled in Groups A and B.

Subjects in all groups will continue to receive treatment until they meet criteria for treatment discontinuation.

Efficacy evaluations will include restaging assessments, physical examination, review of lymphoma symptoms, survival status, and other procedures, as necessary. Disease response by radiologic imaging will be assessed according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007). The exploratory efficacy endpoint of ORR will be assessed according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014).

Efficacy assessments will be performed using computed tomography/magnetic resonance imaging (CT/MRI) scans of the neck, chest, abdomen, and pelvis.

Skull base-to-mid thigh PET scan is recommended but not mandated. Contrast-enhanced MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT or if contrast-enhanced CT scanning cannot be performed due to medical condition(s). For each subject, the modality/modalities utilized at screening will be followed throughout the subject's time on study. While additional modalities may be used depending on assessment needs and disease specifics, technologies used at screening will continue to be followed at each restaging assessment to enable direct comparison with the baseline assessment.

Subjects will have efficacy assessments (CT/MRI) performed at the end of Cycles 2, 4, and 6 (each ± 3 days). If FDG-PET/CT is acquired at baseline, follow-up FDG-PET/CT imaging at Cycle 4 and at Cycle 10 is required. Scans will be sent for a central radiographic review. Subjects who continue to receive CUDC-907 after Cycle 6 will have a disease assessment (CT/MRI) performed every 12 weeks ± 1 week (i.e., Cycles 10, 14, 18) until Cycle 18 in the first 12 months with scans collected through the first year, then every 24 weeks ± 2 weeks (i.e., Cycles 26, 34) until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care).

Safety will be assessed by the incidence and severity of AEs as determined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). Additional safety parameters will include physical examination and vital signs, as well as hematology and serum chemistry laboratory tests (Section 11.2).

8.2. Number of Subjects

Approximately 200 subjects will be enrolled in the study.

8.3. Dose and Schedule

8.3.1. Dose and Mode of Administration

Subjects will receive:

- CUDC-907 60 mg (2 × 30 mg capsules) orally (PO) for 5 days on/2 days off (5/2) (21-day cycles)

CUDC-907 will be administered PO with meals (± 30 minutes). CUDC-907 will be administered in the clinic on days of PK blood sampling, biopsy sampling, and on Day 1 of each cycle up to Cycle 13. Beginning on Cycle 14, in-clinic dosing will only be required on Day 1 of even numbered cycles (i.e., Cycles 14, 16, 18, etc.).

If a dose is missed or vomited, the subject will be instructed to skip that dose and report it to the Principal Investigator (PI) as soon as possible. Missed or vomited doses should not be made up.

Subjects must meet retreatment criteria in order to continue receiving study treatment (see Section 10.5.2).

Treatment delays and dose reductions will be allowed as specified in Section 10.5.3; however subjects who experience a Grade 4 DLT-like event must be discontinued from further study treatment.

For full study treatment details, see Section 10.

8.3.2. Schedule of Visits and Assessments

Treatment and Follow-up Visits are summarized below; for full details see Section 5.1 for the Schedule of Events.

During Treatment: Subjects will have 4 clinic visits during Cycle 1 (Days 1, 5, 12, and 15) and clinic visits every 3 weeks on Day 1 of every cycle thereafter. Subjects who continue past Cycle 13 will have clinic visits every 6 weeks on Day 1 of every other cycle (Cycles 14, 16, 18, etc.).

Safety assessments will be conducted at each clinic visit.

Subjects will have efficacy assessments (CT/MRI) performed at the end of Cycles 2, 4, and 6 (each ± 3 days). If FDG-PET/CT is acquired at baseline, follow-up FDG-PET/CT imaging at Cycle 4 and at Cycle 10 is required. Scans will be sent for a central radiographic review. Subjects who continue to receive CUDC-907 after Cycle 6 will have a disease assessment (CT/MRI) performed every 12 weeks ± 1 week (i.e., Cycles 10, 14, 18) until Cycle 18 in the first 12 months with scans collected through the first year, then every 24 weeks ± 2 weeks (i.e., Cycles 26, 34) until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care).

During Post-Treatment Follow-Up: All subjects will have PFS and survival assessments every 12 weeks during the first 6 months, then every 24 weeks until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care). Overall survival may be checked by phone every 3 months and data entered in the electronic case report form (eCRF).

8.4. Planned Duration of Treatment

CUDC-907 will be taken until disease progression, withdrawal from study, unacceptable toxicity, pregnancy, initiation of another anticancer or experimental therapy, noncompliance with study procedures, or study discontinuation.

Dose and/or schedule intensity of CUDC-907 may be reduced due to toxicity.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1. Patient Inclusion Criteria

1. Age ≥ 18 years.
2. At least 2 but no more than 4 prior lines of therapy for the treatment of *de novo* DLBCL and ineligible for (or failed) autologous or allogeneic SCT (salvage therapy, conditioning therapy and maintenance with transplant will be considered one prior treatment).

   NOTE: For follicular lymphoma transformed to DLBCL (t-FL/DLBCL), single agent non-cytotoxic therapy will not be considered as a line of therapy.
3. Histopathologically confirmed diagnosis of one of the following:
   - RR DLBCL per the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors (Swerdlow et al, 2008).
   - HGBL, with MYC and BCL2 and/or BCL6 rearrangements or DLBCL, NOS per the 2016 revision of the WHO classification of lymphoid neoplasms (Swerdlow et al, 2016).
   - Diagnosis of t-FL/DLBCL is allowed. However, other B-cell lymphomas including other transformed indolent lymphomas/DLBCL per the 2008 WHO classification, HGBL, NOS per the 2016 WHO classification, and Burkitt lymphoma are not eligible.
4. Confirmed availability of viable tissue (defined as most recent available archival tumor tissue available, or fresh tumor samples) for central laboratory FISH and IHC testing prior to study dosing. For subjects who enter the study with unconfirmed MYC-altered disease, fresh tumor samples are preferred.

   NOTE: To facilitate early testing of MYC status, a separate informed consent form (ICF) specific for MYC testing will be available to be signed prior to sample testing and the signing of the main ICF.
5. CT scan showing at least 1 or more clearly demarcated lymph node(s) with a long axis > 1.5 cm and short axis > 1.0 cm **or** 1 clearly demarcated extranodal lesion(s) with a long axis > 1.0 cm and short axis > 1.0 cm. Baseline FDG-PET scans, if used, must demonstrate positive lesions compatible with CT-defined anatomical tumor sites.
6. Presence of RR disease per Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007).
   - Relapsed disease is defined by DLBCL confirmed by excisional/incisional biopsy (preferred) or fine needle aspiration (FNA) or core needle biopsy (CNB) after a CR or unconfirmed complete response (CRu).
     - For relapse during prior treatment, biopsy/FNA reconfirmation of the lymphoma is recommended but not mandatory.
   - Refractory disease is defined by (a) PD during prior treatment, (b) stable disease (SD) after ≥ 3 cycles of prior treatment, or (c) PR after ≥ 6 cycles of prior treatment, or for stage II disease, ≥ 3 cycles of treatment and definitive involved field radiotherapy.

- For sustained PR after prior treatment, confirmation biopsy for DLBCL is preferred. An FNA may be acceptable, but if inappropriate (e.g., due to biopsy inaccessibility), the Sponsor may determine eligibility following review of imaging results and disease history.
- For SD or PD after prior treatment, reconfirmation of DLBCL by biopsy (preferred) or FNA is recommended but not mandatory.

7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
8. Recovery to Grade 1 or baseline of any toxicity due to prior anticancer therapies (excluding alopecia).
9. Absolute neutrophil count (ANC) ≥ 1,000/μL; platelets ≥ 75,000/μL; creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/minute as determined by Cockcroft-Gault (using actual body weight) or by 24-hour urine collection measurements of creatinine; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 × ULN; total bilirubin ≤ 1.5 × ULN or ≤ 3 ULN for patients with documented Gilbert's syndrome. Platelet transfusions and administration of granulocyte colony-stimulating factors to help patients meet eligibility criteria are not allowed within 1 week prior to screening complete blood count (CBC) and Cycle 1, Day 1 treatment.
10. Women of childbearing potential must have a negative serum or urine pregnancy test (not applicable after bilateral oophorectomy)
11. Men and women of childbearing potential and their partners must agree to use adequate birth control throughout their participation in the study and for 30 days following the last study treatment. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence. Acceptable methods of contraception are described in Table 3.
12. In the Investigator's judgement, able to provide written informed consent and follow protocol requirements.

9.2. Patient Exclusion Criteria:

1. Known primary mediastinal, ocular, epidural, testicular or breast DLBCL.
2. Patients must not have active CNS involvement of their malignancy. Patients with prior brain metastases are permitted, but must have completed treatment and have no evidence of active CNS disease (clear cerebrospinal fluid [CSF]) for at least 4 weeks prior to the first dose of CUDC-907. Intrathecal chemoprophylaxis to prevent the emergence or recurrence of lymphoma in the CNS is permitted on study and may be administered per institutional guidelines.
3. Known allergy or hypersensitivity to PI3K inhibitors or any component of the formulations used in this study.
4. Cytotoxic anticancer therapy (e.g., alkylating agents, anti-metabolites, purine analogues) within 2 weeks of study entry.
5. Radiotherapy delivered to non-target lesions within one week prior to starting study treatment or delivered to target lesions that will be followed on the study (note: prior sites of radiation will be recorded).

6. Treatment with experimental therapy within 5 terminal half-lives ($t_{1/2}$) or 4 weeks prior to enrollment, whichever is longer.
7. Current or planned glucocorticoid therapy, with the following exceptions:
    - Doses ≤ 1 mg/kg/day prednisolone or equivalent glucocorticoid and inhalational therapies for mild chronic obstructive pulmonary disease (COPD) or asthma are allowed.
    - Replacement dosing of steroids (defined as < 30 mg/day hydrocortisone or the equivalent) is allowed, provided that the steroid dose has been stable or tapering for at least 14 days prior to the first dose of CUDC-907.
8. Graft versus host disease following transplant within 100 days prior to study treatment.
9. Major surgery, other than diagnostic surgery, occurring 4 weeks prior to study treatment.
10. Diabetes mellitus that is not controlled with medication.
11. Serious infection requiring intravenous antibiotic therapy within 14 days prior to study treatment.
12. Uncontrolled or severe cardiovascular disease, including myocardial infarction, unstable angina, or atrial fibrillation (AFib) within 6 months prior to study treatment, New York Heart Association (NYHA) Class II or greater congestive heart failure, serious arrhythmias requiring medication for treatment, clinically significant pericardial disease, cardiac amyloidosis, or QTc with Fridericia's (QTcF) correction that is unmeasurable or ≥ 480 msec on screening electrocardiogram (ECG). (Note: for QTcF ≥ 480 sec on the screening ECG, the ECG may be repeated twice at least 24 hours apart; the mean QTcF from the three screening ECGs must be < 480 msec in order to meet eligibility for trial participation).
13. Gastrointestinal disease or disorder that could interfere with the swallowing, oral absorption, or tolerance of CUDC-907. This includes uncontrolled diarrhea (> 1 watery stool/day), major abdominal surgery, significant bowel obstruction and/or gastrointestinal diseases that could alter the assessment of PK or safety, including but not limited to: irritable bowel syndrome, ulcerative colitis, Crohn's disease and hemorrhagic coloproctitis.
14. History of other invasive malignancy, unless adequately treated with curative intent and with no known active disease present within 1 year prior to the first dose of study drug, provided it is deemed to be at low risk for recurrence by the treating physician.
    - These conditions include but are not limited to non-melanoma skin cancer, carcinoma *in situ*, (including superficial bladder cancer), cervical intraepithelial neoplasia and organ-confined prostate cancer.
15. Known infection with human immunodeficiency virus (HIV).

16. Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
    - Regardless of hepatitis B surface antigen (HBsAg) status, if hepatitis B core antibody (HBcAb) is positive, then HB DNA testing will be performed and if positive the patient will be excluded.
    - Regardless of hepatitis RNA level, patients who are positive for hepatitis C antibody (anti-HCV) will be permitted to enroll provided that they meet all eligibility criteria and are without evidence of cirrhosis. Patients diagnosed with HCV < 6 months prior to enrollment will be considered to have acute HCV and excluded unless viral load is undetectable.
17. Pregnant or breast-feeding women.
18. Unstable or clinically significant concurrent medical condition that would, in the opinion of the Investigator, jeopardize patient safety and/or compliance with the protocol.

9.3. Criteria for Study Termination

9.3.1. Withdrawal of Subject from Study Treatment

Subjects will be discontinued from further study treatment in the event of any of the following:

- Unmanageable toxicity per Section 10.5.2.
- Subject's decision/withdrawal of consent (e.g., subject declines further treatment).
- Physician decision that continuation is not in the subject's best interest.
- Termination of the study by the Sponsor.
- Other reasons (e.g., major protocol violation, noncompliance).
- Progressive disease.

If the subject is withdrawn from the study the primary reason must be recorded in the eCRF. If possible, the Investigator should arrange for the EOT visit assessments to be completed.

9.3.2. Early Study Termination

The Sponsor has the right to close the study at any time, although this should occur only after mutual consultation between the Sponsor and the Investigators. Events that may trigger early study termination include but are not limited to:

- Insufficient efficacy following interim analyses of Groups A and B.
- Significant toxicity finding.
- Insufficient bioavailability to achieve adequate study drug exposure.
- Change in development plans for the study drug.
- Slow recruitment.

A Safety Review Committee (SRC) comprised of the Medical Monitor, PI, and Sponsor representatives will be convened to review safety information on an ongoing basis for safety

surveillance. The SRC is tasked with making a recommendation to continue or stop the trial based on their assessment of available efficacy and safety information.

An initial review of safety data will be conducted by the SRC including all treated patients after the first 15 patients have completed at least one cycle of treatment. Additionally, any treatment-related deaths will be cause for pausing enrollment and initiating SRC review of all safety data.

The SRC will be tasked with making a recommendation to continue or stop the trial based on their assessment of the benefits or risks to patients based on all available safety information including:

- Grade ≥ 3 toxicity regardless of relationship to treatment
- Treatment discontinuation due to toxicity
- Dose reduction due to toxicity
- Death regardless of cause

Guidelines for stopping criteria are as follows:

- If a third or more of the patients have treatment-related Grade ≥ 3 toxicity, excluding:
  - Grade ≥ 3 thrombocytopenia that resolves (Grade < 3) within 7 days
  - Grade ≥ 3 diarrhea that resolves (to Grade < 3) with standard therapy
- > 10% incidence of colitis, pneumonitis, or severe hepatotoxicity
- > 10% deaths due to Grade 4 treatment-related toxicity

10. TREATMENT OF SUBJECTS

10.1. Description of Study Drug

CUDC-907 mesylate is a synthetic small molecule inhibitor of HDAC and PI3K. The chemical structure of CUDC-907 integrates the hydroxamic acid moiety of HDAC inhibitors into a morpholinopyrimidine pharmacophore of PI3K inhibitors.

CUDC-907 is manufactured, labeled and packaged in accordance with Good Manufacturing Practices (GMP).

CUDC-907 mesylate oral capsules are formulated with three excipients: silicified microcrystalline cellulose (Prosolv® HD90), sodium starch glycolate (Explotab®), and magnesium stearate. The resulting dry blended mixture is filled into gelatin capsule shells.

10.2. Supply, Packaging and Labeling

CUDC-907 will be supplied as gelatin capsules containing 30 mg CUDC-907 and excipients.

The capsules are packaged in high-density polyethylene bottles containing 35 capsules each, and appropriately labelled for clinical trial use as per national regulatory requirements.

10.3. Storage and Dispensing

The study drug should be stored at room temperature in a secure area with access limited to the Investigator and authorized site staff.

Only subjects enrolled in the trial may receive investigational product. The investigational materials are to be prescribed only by the PI or the sub-Investigators named in FDA Form 1572. In addition, the study drug may only be dispensed by authorized personnel at the institution(s) specified on Form 1572. For self-administration, subjects may be provided with a sufficient number of capsules as are needed for 1 cycle of study drug administration.

Under no circumstances is the investigational drug to be used other than as directed within this study protocol.

10.4. Investigational Product Accountability

Study drug accountability records will be maintained throughout the course of the study. The Investigator or designee will document the amount of study drug received, the amount dispensed to study subjects and the amount destroyed locally.

Unused study drug remaining at the completion of the study will be destroyed at the site per institutional standard operating procedures provided that destruction is documented.

10.5. Study Drug Administration

10.5.1. CUDC-907

Subjects will receive CUDC-907 60 mg in 21-day cycles.

CUDC-907 will be administered orally at the assigned dose level and schedule, 60 mg on a 5/2 schedule.

All doses of study drug (in clinic and self-administered) will be administered with meals (± 30 minutes) at approximately the same time each dosing day, if possible.

Dose and/or schedule intensity of CUDC-907 may be reduced per protocol due to toxicity.

In the absence of significant toxicity, each subject is expected to complete at least 1 cycle (21 days) of study treatment. However, subjects may continue to receive additional 21-day cycles of CUDC-907 treatment until disease progression has been documented or other discontinuation criteria have been met (Section 9.3.1).

10.5.2. Retreatment Criteria

Subjects may continue to receive 21-day cycles of study treatment until disease progression has been documented or other discontinuation criteria have been met (Section 9.3.1).

To continue dosing of CUDC-907 subjects must meet the following criteria:

- ANC > 1,000/μL.
- Platelets ≥ 50,000/μL.
- AST and ALT ≤ 2.5 × ULN.
- Bilirubin concentration ≤ 1.5 × ULN (or ≤ 3 ULN for patients with documented Gilbert's syndrome).
- Creatinine ≤ 1.5 × ULN.
- ≤ Grade 2 diarrhea controlled by antidiarrheal treatment.

10.5.3. Safety Criteria for Adjustment or Stopping CUDC-907

10.5.3.1. Dose Delays and Discontinuation of CUDC-907

In the event that any of the above criteria are not met, study drug dosing must be held until the retreatment criteria are met. Treatment may then resume at the full dose of CUDC-907, as long as none of the criteria in Table 2 are met. Beyond Cycle 1, subjects held for > 7 days may restart treatment after the subject has met the above criteria and following discussion and agreement between the Investigator and the Medical Monitor. Beyond Cycle 2, subjects may have study drug held for up to 7 days between the end of a cycle and initiation of another (e.g., Cycle 2 Day 21 to Cycle 3 Day 1). This hold will be at the discretion of the Investigator and after discussion and agreement between the Investigator and Medical Monitor.

Study treatment should be discontinued in the event of an unacceptable toxicity or treatment hold lasting more than 4 weeks, except in cases of clinical benefit determined by the Investigator with approval by the Sponsor Medical Monitor.

Subjects who experience a DLT-like event will be either discontinued from further study treatment or their dose will be reduced following discussion and agreement between the Investigator and the Sponsor's Medical Monitor. A DLT-like event will be defined as any of the following AEs occurring at any time:

- Non-hematological ≥ Grade 3 AE, other than Grade 3 nausea or Grade 3 vomiting in subjects treated with less than optimal antiemetic therapy.
- An AE resulting in a dose delay of ≥ 7 consecutive days (e.g., 6 consecutive missed doses).
- Grade 4 neutropenia ≥ 7 days, or ≥ Grade 3 neutropenia with fever > 101.3ºF (38.5ºC) or ≥ Grade 3 neutropenia with infection.
- Grade 4 thrombocytopenia ≥ 7 days, or ≥ Grade 3 thrombocytopenia and significant bleeding.

NOTE: A DLT-like event excludes AEs that are clearly and incontrovertibly related to the underlying disease or extraneous factors.

10.5.3.2. CUDC-907 Dose Reductions

Table 1: Dose Reduction Steps for CUDC-907

Reduction Steps:	**Schedule**	**Dose**
Starting dose	5/2	60 mg
Dose Reductions	**Schedule**	**Dose**
First dose reduction	4/3	60 mg
Second dose reduction	5/2	30 mg
Final dose reduction	4/3	30 mg

4/3 = 4 days on/3 days off; 5/2 = 5 days on/2 days off

10.5.3.3. Dose Adjustments for CUDC-907 Hematologic and Non-hematologic Toxicity

The administration of HDAC and PI3K inhibitors has been associated with predictable bone marrow suppression that is typically transient and reversible.

The administration of HDAC and PI3K inhibitors has also been associated with hyperglycemia. This hyperglycemia does not generally result in severe metabolic complications and typically resolves with therapeutic intervention. The treatment goal for glycemic control is fasting plasma glucose < 160 mg/dL; while making every attempt to avoid hypoglycemia. Dose modifications of CUDC-907 are based on the severity of toxicities.

CUDC-907 dose adjustments for hematologic and non-hematologic toxicities are shown in Table 2.

Table 2: CUDC-907 Dose Adjustments for Hematologic and Non-Hematologic Toxicities			
Thrombocytopenia	**Grade 1 or 2** No change in dose	**Grade 3 or 4 (platelets < 50,000/µL)** Hold treatment until platelets ≥ 50,000/µL or baseline, then reduce dose to the next lower dose level (as applicable per Table 1).	**Grade 4 thrombocytopenia requiring platelet transfusion** Hold treatment until platelets ≥75,000/µL or baseline, then dose reduce to the next lower dose level (as applicable per Table 1).
Neutropenia	**Grade 1 or 2** No change in dose	**Grade 3 or 4 (ANC < 1,000/uL)** Hold treatment until ANC ≥ 1000/µL, then reduce dose to the next lower dose level (as applicable per Table 1).	**Grade 4 febrile (≥ 38.5° C) neutropenia** Hold treatment until febrile neutropenia resolves and ANC ≥ 1000/µL or baseline, then dose reduce to the next lower dose level (as applicable per Table 1).
Anemia	**Grade 1 or 2** No change in dose	**Grade 3 or 4 (hemoglobin < 8 g/dL)** Hold treatment until hemoglobin ≥ 10 g/dL or baseline then reduce dose to the next lower dose level (as applicable per Table 1).	**Grade 4 anemia requiring transfusion** Hold treatment until hemoglobin ≥ 10 g/dL or baseline, then dose reduce to the next lower dose level (as applicable per Table 1).
Recurrence of Grade 3 or 4 hematologic toxicity will be cause for a second dose modification. **If the starting dose does not permit dose modification, then study drug will be discontinued.**			
Non-hematological AEs (excluding hyperglycemia)	**Grade 1 or 2** No change in dose[1]	**Grade 3** • Hold treatment until resolution to ≤ Grade 1 or baseline • If not recovered to ≤ Grade 1 or baseline within 3 weeks, reduce to next lower dose level upon return to ≤ Grade 1 or baseline (as applicable per Table 1).	**Grade 4** Discontinue treatment.[2]
Recurrence of Grade 3 non-hematologic toxicity (excluding hyperglycemia) or inability to reduce dose (based on starting dose) will be grounds for discontinuation of study drug.			

Table 2: CUDC-907 Dose Adjustments for Hematologic and Non-Hematologic Toxicities (Continued)

Toxicity	Management		
Hyperglycemia	**Grade 1/2 or Grade 3 (> 250 – 500 mg/dL) asymptomatic** No change in dose[1]	**Grade 3 (> 250 – 500 mg/dL) symptomatic or Grade 4 (> 500 mg/dL)** Hold treatment until glucose < 250 mg/dL and asymptomatic; Reduce dose to the next lower dose level (as applicable per Table 1).	**≥ Grade 3 hyperglycemia not improving despite appropriate treatment for 1 week or symptomatic Grade 4 hyperglycemia (> 500 mg/dL)** Hold treatment until glucose < 250 mg/dL and asymptomatic; Reduce dose to the next lower dose level (as applicable per Table 1) upon return to ≤ Grade 1 or baseline.
Recurrence of Grade 3 or 4 hyperglycemia will be cause for a second dose modification. **If the starting dose does not permit dose modification, then study drug will be discontinued.** **Recurrence of Grade 3 or 4 hyperglycemia that does not recover to ≤ Grade 1 or baseline within 3 weeks after second modification (as applicable) will be grounds for discontinuation of study drug.[2]**			

AEs = adverse events; ANC = absolute neutrophil count

[1] Transient Grade 1 or 2 hyperglycemia should be monitored per Investigator discretion and medical guidelines.

[2] An exception for ongoing treatment may be made in the case of Investigator-determined clinical benefit with approval from the Medical Monitor.

10.6. Concomitant Medications

Information on concomitant medications will be collected from 30 days prior to study drug dosing through the EOT visit. Information on subsequent anticancer treatments will be collected through the Follow-up visits.

10.6.1. Permitted Medications

Antidiarrheal treatment (e.g., loperamide) should be administered immediately upon the first onset of symptoms. Each subject should be instructed to have loperamide or a comparable anti-diarrheal medication (per institutional standard) readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the subject until diarrhea free. Subjects will be instructed to notify the Investigator if diarrhea occurs and will be evaluated in the clinic for significant dehydration, possible electrolyte imbalance, and/or ongoing losses. If clinically significant dehydration is present, rehydration and electrolyte repletion per institutional standard will be required. Additionally, subjects will be monitored following rehydration for the risk of recurrence and electrolyte imbalances and also advised regarding appropriate fluid management to reduce the likelihood of subsequent dehydration events.

Antiemetics may be given prophylactically after the first episode of nausea or vomiting per standard of care at each study center.

Unless otherwise prohibited (See Section 10.6.2), supportive therapy for optimal medical care may be administered per institutional standard of care at the study centers.

Growth factor support is permitted for neutropenia or neutropenic fever.

10.6.2. Drug Interactions/Precautions

In vitro, CUDC-907 competitively inhibits cytochrome P450 isoenzymes CYP2C9, CYP2C19, CYP2D6 and CYP3A4 with half maximal inhibitory concentration (IC_{50}) values of > 10, > 10, > 10, and 0.28 to 13.58 μM, respectively. Currently, it is not known whether achievable plasma exposures of CUDC-907 in humans will approach these *in vitro* determined values. These data suggest that CUDC-907 may inhibit cytochrome P450 isoenzymes CYP2C9, CYP2C19, CYP2D6, and CYP3A4, although the clinical significance of this potential interaction has not been investigated. Subjects receiving concomitant medications metabolized by these enzymes should be monitored at the discretion of the Investigator.

Please refer to the CUDC-907 Investigator's Brochure for additional drug interaction information.

10.6.3. Contraception

Subjects of childbearing potential and their partners must agree to use adequate birth control throughout their participation in the study and for 30 days following the last study treatment for subjects receiving CUDC-907. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.

NOTE: vomiting and diarrhea may cause oral contraceptives to be ineffective.

Table 3: Effective Methods of Contraception

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide plus one additional contraceptive method Cap plus spermicide plus one additional contraceptive method Diaphragm plus spermicide plus one additional contraceptive method	Copper T Progesterone T[1] Levonorgestrel-releasing intrauterine system[1]	Implants Hormonal shot or injection Combined pill Minipill Patch

[1]Also considered hormonal methods of contraception.

10.7. Treatment Compliance

To facilitate and ascertain treatment compliance, subjects may be provided with and trained to complete a Dosing Diary, which must be returned to the clinic for review at each clinic visit.

10.8. Group Allocation

Based on central testing and review, subjects receiving treatment will be classified into one of the following categories for purposes of analysis: (1) Group A: *MYC* translocation^{+} by FISH, (2) Group B: MYC expression in ≥ 40% of tumor cells by IHC and/or *MYC* gene copy number gain by FISH, or (3) Group C: *MYC* translocation^{-} by FISH, and MYC expression in < 40% of tumor cells by IHC, and no *MYC* gene copy number gain by FISH (Figure 1).

To facilitate early testing of MYC status, a separate ICF specific for MYC testing will be available to be signed prior to sample testing and the signing of the main ICF.

All subjects who enter into the Screening period of the study (defined as the point at which the patient signs the main ICF) will receive a unique screening number. Once all eligibility criteria are confirmed and the subject is enrolled in the study, a subject identification number will be assigned. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject.

The study is open-label and therefore no provisions will be made for blinding.

11. STUDY ASSESSMENTS

11.1. Screening

The PIs at each site are responsible for maintaining a record of all screened subjects, including both those who enter the study and those who are excluded. Screening procedures performed as part of standard-of-care, in advance of signing the ICF, need not be repeated for study purposes if performed within the 28-day screening visit window.

11.1.1. Patient Registration and Group Assignment

Inclusion and exclusion criteria will be reviewed for each potential subject. By central testing, the threshold for MYC-altered status is defined as *MYC* translocation^{+} by FISH and/or MYC expression in ≥ 40% of tumor cells by IHC, and/or *MYC* gene copy number gain by FISH. Subjects will be required to submit archival (most recent available) or fresh tumor samples for central FISH and IHC testing. For subjects who enter the study with unconfirmed MYC-altered disease, fresh tumor samples are preferred.

Collection details and shipping address will be provided in the laboratory manual.

Centralized registration and group assignment for eligible subjects will be completed according to a process defined by the Sponsor (Section 10.8).

11.2. Safety Evaluations

11.2.1. Demographics and Medical History

Each patient's complete medical history will be documented during Screening, including demographic information, relevant medical history, current primary cancer diagnosis, and prior cancer treatments (chemo- and immunotherapies, radiation therapy, surgeries).

11.2.2. Physical Exam

A complete physical exam will be performed at Screening, Day 1 of each cycle, and at the EOT visit. Symptom-directed physical exams are required on Days 5 and 12 of Cycle 1 and at the Post-Treatment Follow-up visits (until time of disease progression, withdrawal of consent, or any other criteria that would make the patient unable to be followed for disease response).

11.2.3. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status (scale provided in Appendix A) will be assessed at Screening, Day 1 of each Cycle, and at the EOT visit.

11.2.4. International Prognostic Index (IPI)

The IPI will be performed for each subject at Screening and at Post-Treatment Follow-up visits.

11.2.5. Lymphoma Assessment

Lymphoma assessment, consisting of a physical examination, a review of the subject's current signs and symptoms, B symptoms (drenching night sweats, fevers > 101°F [38.3°C], chills, unexplained weight loss of over 10% of body mass over 6 months), and concomitant medications, will be conducted on Day 1 of every cycle, and at the EOT and Post-Treatment Follow-up visits (until time of disease progression, withdrawal of consent, or any other criteria that would make the subject unable to be followed for disease response).

11.2.6. Vital Signs

Vital signs will include resting supine blood pressure, heart rate, respiratory rate, temperature, and weight (kg). Height will be measured only at Screening. Blood pressure, heart rate, respiratory rate, temperature, and weight will be measured at scheduled visits per protocol (see Schedule of Events in Section 5.1).

11.2.7. Clinical Laboratory Tests

Local laboratories will perform all clinical laboratory tests and results will be provided to the Investigator. Samples will be collected at scheduled study visits before the administration of study drug unless otherwise noted, and more frequently if clinically indicated. In the event of a clinically significant ≥ Grade 2 laboratory toxicity, more frequent laboratory tests should be performed until resolution or stabilization to ≤ Grade 1. After Cycle 1, clinical laboratory tests may be performed within 2 business days prior to scheduled visits.

Hematology tests include complete blood count (hemoglobin, hematocrit, white blood cell [WBC], platelets) with WBC differential (total neutrophils, eosinophils, basophils, lymphocytes and monocytes).

Blood chemistry tests include sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, blood urea nitrogen (BUN), creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose.

In addition, serum LDH will be measured during Screening.

Laboratory tests will be performed at the time points specified in the Schedule of Events (Section 5.1).

11.2.8. Pregnancy Testing

A serum or urine pregnancy test will be performed for female subjects of childbearing potential at Screening, at least once per cycle prior to dosing, and at the EOT visit. The result must be negative for the subject to be enrolled in the study. A positive result observed following enrollment should be confirmed with a repeat serum pregnancy test. Pregnancy tests may be performed more frequently as clinically indicated.

11.2.9. Electrocardiogram

Standard, single 12-lead ECGs at Screening and the EOT visit will include heart rate, respiratory rate, and pulse rate, QRS, and QTcF (Fridericia's formula) intervals. The Investigator will be

responsible for a thorough review of the tracings for any untoward changes from the baseline ECG for each individual subject.

During the screening ECG, if a patient has a QTcF ≥ 480 sec on the screening ECG, the ECG may be repeated twice (at least 24 hours apart) and the mean QTcF from the three screening ECGs must be < 480 msec in order to meet eligibility criteria for trial participation.

During treatment, based on triplicate ECGs, if a patient has a mean QTcF ≥ 480 msec or the mean is an increase from the mean baseline (pretreatment on Day 1 of Cycle 1) QTcF of > 60 msec, the ECG may be repeated 2 more times within 5 minutes. The following will be applied based on the mean of the results for all (up to 5) of the ECGs:

- Continue ECG testing hourly until the increase resolves. If not resolved in 6 hours, discontinue further treatment and refer to in-hospital care.
- If resolved in < 6 hours, resume dosing but repeat the ECG schedule specified above on the next day of dosing.
  - If prolongation of QTcF meeting these criteria occurs again, discontinue further treatment and, if not resolved in 6 hours, refer to in-hospital care.
  - If QTc prolongation does not reoccur, continue treatment as specified in the protocol.

On any ECG if sustained (>3 beats) ventricular tachycardia is detected, the patient should be referred immediately to in-hospital care.

If on any ECG, AFib is detected, the patient should be referred for appropriate cardiology care, and within no more than 6 hours after discharge from the clinic, have Holter monitoring instituted and continued for at least 48 hours. Withhold treatment until review of the Holter results:

- If AFib did not resolve within 3 hours or by the time of the start of the Holter monitoring if longer than 3 hours after discharge from the clinic, discontinue further treatment.
- If during the Holter monitoring AFib was present for > 3 hours, either sustained or as accumulated AFib duration, discontinue further treatment.
- If AFib had resolved within 3 hours or by the time of the start of the Holter monitoring if longer than 3 hours after discharge from the clinic, and did not reoccur in the 48 hours of monitoring, treatment can be resumed.

- On the next day of dosing perform:
  - ECGs per the schedule outlined above.
  - Conduct Holter monitoring for 24 hours starting at least 1 hour prior to the dose.
  - Withhold the subsequent dose until review of the Holter results.
  - If AFib is again detected on ECG or of duration > 30 minutes on Holter monitoring, discontinue treatment.
  - If AFib does not reoccur, continue treatment as specified in the protocol.

11.2.10. Adverse Events

Monitoring and recording of AEs will be conducted throughout the study. Adverse events, including SAEs, will be captured on the case report forms (CRFs) from the first day of study drug dosing until the EOT visit (30 ± 7 days post the last dose of study treatment). After the EOT visit, only treatment-related SAEs will be captured. Treatment-related SAEs that are ongoing at the time of Follow-up visits should continue to be followed until resolution, return to baseline or are deemed the subject's new baseline, or until they are ≤ Grade 1 (and following consultation and agreement by the Medical Monitor). Definitions, documentation, and reporting of AEs are described in detail in Section 12. Following the Follow-up visits, any SAE determined by the Investigator to be potentially related to study treatment must also be reported.

11.2.11. Concomitant Medications and Other Treatments

Information on concomitant medications and other treatments, including blood products, will be collected from 30 days prior to study drug dosing through the Follow-up visits (see Section 10.6) and will be updated at every study visit. Beginning with the Follow-up visits, only anti-cancer therapies will be documented.

11.3. Efficacy Evaluations

11.3.1. Baseline Disease Assessment

Cancer staging procedures should be performed during screening according to Ann Arbor classification (Appendix B), utilizing appropriate modalities for disease assessment such as PET-CT scanning, MRI scans, bone marrow assessment, and/or other laboratory assessments. The subject's most recent tumor samples, either archived or fresh, must be sent to the central laboratory for verification of diagnosis.

For confirmation of relapsed disease (defined as PD after a CR or Cru), biopsy is preferred but FNA is acceptable. For relapse during prior treatment, biopsy/FNA reconfirmation of the lymphoma is recommended but not mandatory.

In subjects with refractory disease (defined as [a] PD during prior treatment, [b] SD after ≥ 3 cycles of prior treatment, or [c] PR after ≥ 6 cycles of prior treatment, or for stage II disease, SD after ≥ 3 cycles of treatment and definitive involved-field radiotherapy) with sustained PR, a confirmation biopsy for DLBCL is preferred but an FNA may be acceptable. If an FNA is inappropriate (e.g., due to biopsy inaccessibility), the Sponsor may determine eligibility

following review of imaging results and disease history. For subjects with SD or PD after prior treatment, reconfirmation of DLBCL by biopsy (preferred) or FNA is recommended but not mandatory.

11.3.2. Disease Response Assessments

The Investigator and independent review committee will evaluate each subject for response to therapy according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007). The independent review committee will be blinded to the investigator's assessment of response.

Efficacy assessments will be performed using CT/MRI scans of the neck, chest, abdomen, and pelvis.

Skull base-to-mid thigh PET scan is recommended but not mandated.

Contrast-enhanced MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT or if contrast-enhanced CT scanning cannot be performed due to medical condition(s).

For each subject, the modality/modalities utilized at screening will be followed throughout the subject's time on study. While additional modalities may be used depending on assessment needs and disease specifics, technologies used at screening will continue to be followed at each restaging assessment to enable direct comparison with the baseline assessment.

The exploratory efficacy endpoint of ORR will be assessed according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014). All subjects on active treatment will have disease response assessments (CT/MRI) performed during the last week (Day 15 – 21) of Cycles 2, 4, and 6 (each ± 3 days). If FDG-PET/CT is acquired at baseline, follow-up FDG-PET is required at Cycle 4 and at Cycle 10. PET findings with score 1 and 2 by 5-PS score are considered as PET-negative and PET findings with score 3, 4, and 5 by 5-PS score are considered as PET-positive. Subjects who continue to receive CUDC-907 after Cycle 6 will have disease response assessments (CT/MRI) performed approximately every 12 weeks ± 1 week (i.e., Cycles 10, 14, 18) until Cycle 18 in the first 12 months with scans collected through the first year, then every 24 weeks ± 2 weeks (i.e., Cycles 26, 34) until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care).

11.3.3. Survival Status

Information on survival status will be collected for all subjects at the Post-Treatment Follow-up Visit time points.

11.4. CUDC-907 Pharmacokinetic Analyses

Subjects will have blood samples collected for the measurement of plasma concentrations of CUDC-907 and its major metabolite(s). For all subjects, samples will be drawn 2 hours post-dose on Day 1 of Cycles 1 and 4, and on Day 1 of every other cycle thereafter (i.e., Day 1 of Cycles 6, 8, 10, etc.). In addition, for the first 50 subjects enrolled on amendment 4, blood samples will also be obtained 2 hours post-dose on Days 8 and 15 of Cycle 1. Blood samples (4

mL) will be collected using lithium heparin plasma tubes (e.g., Becton Dickinson Vacutainers Cat # 367884 or similar). One additional blood sample may be obtained at a later time point to assess for possible study drug accumulation.

A full description of sample handling procedures is included in the laboratory manual.

11.5. Biomarker Assessments

11.5.1. Pharmacogenomic Assessments

PAXgene® blood samples for pharmacogenomic assessment will be collected during the Screening period. Collection details and shipping address will be provided in the laboratory manual.

11.5.2. Plasma Biomarker Assessments

Blood samples (20 mL) for plasma biomarker analysis will be drawn during the Screening period and on Day 1 of scheduled clinic visits per protocol (see Schedule of Events in Section 5.1). The plasma samples will be analyzed for cell-free DNA (cfDNA) and potential markers of CUDC-907 activity, such as changes in cytokine levels.

These time points may be administratively adjusted or discontinued at the discretion of the Sponsor; however, the total number of blood samples will not be increased.

Collection details and shipping address will be provided in the laboratory manual.

11.5.3. Tumor Biomarker Assessments

Optional tumor samples (i.e., CNB or FNA biopsy samples for subjects with accessible lesions) may be obtained prior to the first dose and within 8 hours post-dose on Cycle 1, Day 15 through Cycle 2, Day 1. If available, archival tumor tissue samples and corresponding pathology report will also be collected. Samples will be analyzed to evaluate baseline levels and/or changes in biomarkers related to the disease and/or targeted pathways, if feasible. BCL2 and BCL6 expression and gene translocation status are among disease-related biomarkers to be tested.

Collection details and shipping address will be provided in the laboratory manual.

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1. Definition of an Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug from any route of administration, formulation, or dose, including an overdose.

An AE includes:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen in severity or frequency
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention, dose hold, dose reduction or schedule change. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the Laboratory section of the clinical study report.

Disease progression is a worsening of a subject's condition attributable to the disease for which the study medication is being given. This may be an increase in severity of the disease or an increase in the symptoms of the disease. New or increasing signs and symptoms related to disease progression should be reported as an AE; however, disease progression and death from disease progression should not be recorded as an AE unless death occurs within 30 days of the subject's last dose of CUDC-907.

12.2. Recording Adverse Events

All AEs will be reported from the first dose of study drug through the EOT visit (30 ±7 days following the last day of study treatment). Only treatment-related AEs will be captured from

EOT through Follow-up visits. All treatment-emergent SAEs will be followed until resolution or stabilization.

Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). AE reporting and severity grading will be assessed using the NCI Common Toxicity Criteria (CTC), Version 4.03 (June 2010). For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate and severe into CTCAE grades should be used. A copy of the NCI CTC is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

The causal relationship to study treatment will be determined by the Investigator according to best medical judgment, as follows:

- Definitely related: This category applies when, after careful medical consideration, there is almost no consideration of other causation.
- Probably related: There is a clinically plausible time sequence between onset of the AE and study treatment administration. The AE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study drug.
- Possibly related: There is a clinically plausible time sequence between onset of the AE and study treatment administration, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding study drug withdrawal may be lacking or unclear. "Possible" should be used when study treatment administration is one of several biologically plausible causes of the AE.
- Unlikely related: The AE is most likely due to a non-study-treatment-related cause. However, association with the study treatment cannot be completely ruled out.
- Unrelated: Another cause of the AE is most plausible and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study treatment administration and/or a causal relationship is considered biologically implausible.

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

12.3. Serious Adverse Events

An SAE is any AE or suspected adverse reaction that is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Is fatal;
- Is life-threatening (defined as an immediate risk of death from the event as it occurred);
- Requires in-patient hospitalization or prolongation of existing hospitalization (Exception: Hospitalization for elective treatment of a pre-existing condition that did

not worsen during the study and is not considered an AE. Note: Complications that occur during hospitalization are AEs and if a complication prolongs hospitalization, then the event is serious);

- Results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly/birth defect, or;
- Though not included in the above definitions, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of important medical events which may meet the definition of a SAE include: intensive treatment in the emergency room or at home for allergic bronchospasm, certain abnormalities (e.g., blood dyscrasias), convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Grade 4 laboratory abnormalities will not be reported as SAEs except in those cases when the abnormality is associated with a clinical diagnosis, which is a recorded SAE.

12.4. Reporting of Adverse Experiences, Serious Adverse Experiences, Serious and Unexpected Adverse Experiences

12.4.1. Reporting Adverse Events and Serious Adverse Events to the Sponsor

All SAEs, regardless of relationship to the study treatment, must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event. Written SAE notification must follow within the 24-hour reporting timeframe, via an SAE Report submitted to Novella Clinical Safety Management via email at pvgsafety@novellaclinical.com or by fax at 1-866-761-1275. Where appropriate, follow-up SAE reports must be submitted by the Investigator as new information becomes available. All treatment-emergent SAEs should be followed until resolution, return to baseline or stabilization.

If the Investigator becomes aware of safety information involving a subject who participated in the study that appears to be drug related, even after an individual subject has completed the study, this should also be reported to the Sponsor.

12.4.2. Reporting to the Institutional Review Board (IRB)

SAEs will be reported to the IRB by the Investigator according to local or national requirements and the IRB's policy and procedures.

12.4.3. Reporting to the Regulatory Authorities

The Sponsor will be responsible for reporting all AEs and SAEs to the appropriate regulatory authority (e.g., U.S. FDA), Investigators, and central IRB in accordance with all applicable regulations and guidances.

12.4.4. Pregnancy Reporting

Pregnancy testing must be performed in all female subjects of childbearing potential at Screening, at least once per cycle prior to dosing, at the EOT visit, and as clinically indicated. In the event of a positive test result, subjects will be discontinued from study drug and will be followed for the outcome of their pregnancy.

If a female subject suspects she might be pregnant (e.g., missed or late menstrual period) or a male subject suspects he may have fathered a child at any time during the study through the final Follow-up visit, they must notify the Investigator immediately. The Investigator will follow the subject or subject's partner to determine the outcome of the pregnancy.

Information regarding pregnancy must be reported immediately to the Sponsor and the outcome information provided once the outcome is known.

The Investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The Investigator should follow-up with the subject or subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (see Section 12.3).

13. STUDY ACTIVITIES

During the treatment period, all treatment assessments/procedures should occur within ± 2 days of the scheduled time points. If extenuating circumstances prevent a subject from starting or completing treatment, or a scheduled procedure or assessment within the protocol-specified time, the subject may continue to be treated on the study only with permission of the Curis Medical Monitor or designee clinician.

All times should be recorded using the 24-hour clock (e.g., 23:20, rather than 11:20 PM).

13.1. Prescreening (Before Day -28) and Screening (Days -28 to -1)

The following procedures may be performed between Days -28 and -1:

- Informed consent
    - Based on local site requirements, the following ICF procedures are acceptable:
        - An ICF specific for MYC testing will be signed before the tumor sample is sent for central testing (Prescreening).
        - The main ICF will be signed to begin the Screening period (Day -28 to Day -1).
- Review inclusion/exclusion criteria
- Subject demographics, medical history, and medication history
- Obtain archival or fresh tumor sample (preferred) for central FISH and IHC testing and review
    - If archival, it must be the most recently available tumor sample
    - Fresh tumor tissue should be obtained from biopsy-accessible lesions with low estimated risk for serious complications (less than 2%)
    - Local MYC results performed previously should be entered into the eCRF at screening although central testing is required for all patients
- IPI score
- Radiologic assessment (CT/MRI and FDG-PET/CT, if applicable)
- Urinalysis
- Collect plasma for biomarker sampling
- Optional tissue collection for biomarker sampling (from subjects with accessible tumor lesion) (may be obtained anytime up to pre-dose Cycle 1, Day 1)
- Pharmacogenomic sampling
- Update concomitant medications

13.1.1. Days -7 to -1

A second set of screening procedures may be performed between Days -7 to -1:

- Physical examination
- Determine ECOG performance status
- Obtain height and vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight)
- ECG
- Pregnancy test (women of childbearing potential)
  - A serum or urine pregnancy test will be performed during Screening, as well as at least once per cycle prior to dosing or more frequently as clinically indicated, and at the End of Therapy (EOT) visit.
- CBC with differentials
- Serum chemistries to include sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose.
- Update concomitant medications

13.2. Treatment Period (Cycle 1 to End of Therapy Visit)

Note: Physical exam, performance status, vital signs including weight, CBC w/differentials and serum chemistry labs may be performed up to 3 days prior to Day 1 of each cycle.

Pregnancy tests (serum or urine) will be performed for women of childbearing potential at least once per cycle prior to dosing, or more frequently as clinically indicated, as well as during Screening and at the EOT visit.

13.2.1. Cycle 1

13.2.1.1. Cycle 1, Day 1

The following procedures will be performed on Cycle 1, Day 1:

- Physical examination
  - Note: The Cycle 1, Day 1 physical examination is not required if the Screening physical examination was conducted within 3 days prior to administration of the first dose of study drug (Cycle 1, Day 1).
- Update ECOG performance status
- Vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight)
- Lymphoma assessment (includes physical examination, a review of the subject's current signs and symptoms, B symptoms, and concomitant medications)
- CBC with differentials

- Serum chemistries (sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose)
- Pregnancy test (women of childbearing potential)
- Collect plasma for PK sampling (2 hours post-dose)
  - CUDC-907 will be administered in the clinic on PK sampling days
- Update concomitant medications
- Collect AEs
- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.1.2. Cycle 1, Days 2-4, Days 8-11, Days 16-19

- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.1.3. Cycle 1, Days 5 and 12

The following procedures will be performed on Cycle 1, Days 5 and 12:

- Symptom-directed physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight)
- CBC with differentials
- Serum chemistries (sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose)
- Update concomitant medications
- Collect AEs
- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.1.4. Cycle 1, Day 8

- Collect plasma for PK sampling (2 hours post-dose, for first 50 subjects enrolled on amendment 4)
  - CUDC-907 will be administered in the clinic on PK sampling days

13.2.1.5. Cycle 1, Day 15

The following procedures will be performed on Cycle 1, Day 15:

- Optional tissue collection for biomarker sampling (from subjects with accessible tumor lesion) may be obtained within 8 hours post-dose on any dosing day from Cycle 1, Day 15 through Cycle 2, Day 1.
  - CUDC-907 will be administered in the clinic on tissue sampling days

- Update concomitant medications
- Collect AEs
- Collect plasma for PK sampling (2 hours post-dose, for first 50 subjects enrolled on amendment 4)
- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.2. Cycles 2 through 6

13.2.2.1. Cycles 2 through 6, Day 1

The following procedures will be performed on Day 1 of Cycles 2 through 6:

- Physical examination
- Update ECOG performance status
- Vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight)
- Lymphoma assessment (includes physical examination, a review of the subject's current signs and symptoms, B symptoms, and concomitant medications)
- Radiologic assessment (CT/MRI are required at the end of Cycle 2 (± 3 days), Cycle 4 (± 3 days) and Cycle 6 (± 3 days). If FDG-PET/CT is acquired at baseline, follow-up FDG-PET/CT imaging at Cycle 4 is required)
- CBC with differentials
- Serum chemistries (sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose)
- Pregnancy test (women of childbearing potential)
- Collect plasma for biomarker sampling
- Collect plasma for PK sampling on Cycle 4, Day 1 only (2 hours post-dose)
  - CUDC-907 will be administered in the clinic on PK sampling days.
- Update concomitant medications
- Collect AEs
- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.2.2. Cycles 2-6, Days 2-5, Days 8-12, Days 15-19

- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.3. Cycles 7+

Note: Subjects who continue past Cycle 13 will only be required to have a Day 1 visit at the beginning of every other cycle (14, 16, 18, etc.).

13.2.3.1. Cycles 7+, Day 1

The following procedures will be performed on Day 1 of Cycles 7+:

- Physical examination
- Update ECOG performance status
- Vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight)
- Lymphoma assessment (includes physical examination, a review of the subject's current signs and symptoms, B symptoms, and concomitant medications)
- Radiologic assessment (CT/MRI [If FDG-PET/CT is acquired at baseline, follow-up FDG-PET/CT imaging at Cycle 10 is required])
- CBC with differentials
- Serum chemistries (sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose)
- Pregnancy test (women of childbearing potential)
- Collect plasma for biomarker sampling
- Update concomitant medications
- Collect AEs
- Collect plasma for PK sampling (2 hours post-dose) every other cycles (i.e., Cycles 6, 8, 10, etc.)
  - CUDC-907 will be administered in the clinic on PK sampling days.
- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.3.2. Cycles 7+, Days 2-5, Days 8-12, Days 15-19

- CUDC-907 dosing (CUDC-907 is taken PO for 5 days on/2 days off)

13.2.4. End of Therapy Visit (Day 30)

The following procedures will be performed at the EOT visit:

- Physical examination
- Update ECOG performance status
- Vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight)
- ECG
- Pregnancy test (women of childbearing potential)
  - A serum or urine pregnancy test will be performed at the EOT visit, as well as during Screening and at least once per cycle prior to dosing, or more frequently as clinically indicated.

- Lymphoma assessment (includes physical examination, a review of the subject's current signs and symptoms, B symptoms, and concomitant medications)
  - Done only if not performed within 4 weeks of the EOT visit
- Radiologic assessment (CT/MRI)
  - Done only if not performed within 4 weeks of the EOT visit
- CBC with differentials
- Serum chemistries (sodium, potassium, magnesium, phosphate, total protein, chloride, bicarbonate, calcium, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin, and glucose)
- Update concomitant medications
- Collect AEs

13.3. Post-Treatment Follow-up Visits

13.3.1. Follow-up Visits ≤ 6 Months (Every 12 Weeks)

- Symptom-directed physical examination (performed until time of disease progression, withdrawal of consent, or any other criteria that would make the subject unable to be followed for disease response)
- IPI score
- Lymphoma assessment (includes physical examination, a review of the subject's current signs and symptoms, B symptoms, and concomitant medications)
- Radiologic assessment (CT/MRI)
- Survival status
- Update concomitant medications (anti-cancer therapies only)
- Collect AEs (only treatment-related SAEs will be captured)

13.3.2. Follow-up Visits > 6 Months (Every 24 Weeks)

- Symptom-directed physical examination (performed until time of disease progression, withdrawal of consent, or any other criteria that would make the subject unable to be followed for disease response) and updated
- IPI score
- Lymphoma assessment (includes physical examination, a review of the subject's current signs and symptoms, B symptoms, and concomitant medications)
- Radiologic assessment (CT/MRI)
- Survival status
- Update concomitant medications (anti-cancer therapies only)

- Collect AEs (only treatment-related SAEs will be captured)

14. STATISTICAL ANALYSES

14.1. Overview of Study Design

The safety and preliminary efficacy of CUDC-907 will be evaluated when administered in subjects with RR MYC-altered DLBCL. Patients with RR DLBCL will be tested for MYC-altered disease, defined as *MYC* translocation by FISH, or MYC expression in ≥ 40% of tumor cells by IHC staining and/or *MYC* gene copy number gain by FISH based on fresh or archived tumor tissue sample (most recent available).

Based on central testing and review, subjects will be classified into one of the following categories: (1) Group A: *MYC* translocation^{+} by FISH, (2) Group B: MYC expression in ≥ 40% of tumor cells by IHC and/or *MYC* gene copy number gain by FISH, or (3) Group C: *MYC* translocation^{-} by FISH and MYC expression in < 40% of tumor cells and no *MYC* gene copy number gain by FISH.

Subjects in all groups will continue to receive treatment until they meet criteria for treatment discontinuation.

14.2. Study Endpoints

14.2.1. Primary Endpoint

- ORR (central determination)

14.2.2. Secondary Endpoints

- ORR (local determination)
- PFS, median PFS, and PFS6 (central and local determination)
- OS
- DCR and DOR (central and local determination)
- To evaluate the incidence and severity of AEs, SAEs, and other safety parameters in subjects receiving CUDC-907.
- To characterize the PK of CUDC-907.

14.2.3. Exploratory Endpoints

- To explore the effects of CUDC-907 on disease-associated biomarkers.
- To explore the relationship between disease-associated biomarkers in plasma and tumor tissue. Among biomarkers of interest, BCL2 and BCL6 protein expression and translocation status in particular will be tested in tumor tissue, where possible.
- To explore biomarkers of response for patient selection.
- To explore the relationship between additional biomarkers and biomarker profiles that may influence biologic and clinical responses to CUDC-907.

- To explore the ORR according to Lugano classification (Cheson et al, 2014; Barrington et al, 2014).

14.3. Sample Size Considerations

The sample size for Groups A and B was determined based on the following:

With a sample size of 50 subjects in Groups A and B with an ORR of 30.0%, a two-sided 95% confidence interval employing the exact binomial method will extend from 17.9% to 44.6%. This confidence bound (CB) about the observed ORR is thought to adequately characterize the disease response of these populations after receiving CUDC-907.

Below are the 95% confidence intervals for various response rates using a sample size of 50 subjects and employing the exact binomial methodology.

Sample Size	ORR	Lower 95% Confidence Bound	Upper 95% Confidence Bound
50	15 (30%)	17.9%	44.6%
50	14 (28%)	16.2%	42.5%
50	13 (26%)	14.6%	40.4%
50	12 (24%)	13.1%	38.2%)

Enrollment within a group or overall may also terminate early due to other considerations such as those that may preclude timely completion of the study (e.g., low prevalence of MYC-altered DLBCL).

14.4. Statistical Analysis

The statistical analyses will be performed using SAS® version 9.4 or later (SAS Institute Inc., Cary, NC). A comprehensive statistical analysis plan (SAP) will be finalized prior to database lock.

14.4.1. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all subjects in Groups A and B. The primary analyses of efficacy will be conducted based on the ITT Population.

The Evaluable Population will consist of all subjects in Groups A and B who receive at least one full cycle of treatment and have at least one post-baseline disease assessment and have not had major protocol deviations that are thought to have materially impacted efficacy outcomes. Major protocol deviations will be identified prior to database lock. Secondary analysis of efficacy will also be conducted based on the Evaluable Population. In addition, the primary efficacy endpoint (ORR) will also be assessed using the Evaluable Population as a secondary analysis.

The Safety Population will consist of all subjects who receive any treatment. All safety analyses will be conducted based on this population.

14.4.2. Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as sex, age, race, and weight, as well as disease-specific characteristics, such as tumor stage and histology.

14.4.3. Efficacy Analyses

The primary analyses of efficacy will be based on the ITT Population. The interim analyses will be performed on the Evaluable Population.

The primary efficacy endpoint, ORR, will be based on the proportion of subjects with CR or PR using the central determination of disease response in Groups A and B, separately. The estimate will be accompanied by a two-sided exact binomial 95% CB.

Progression-free survival, OS, and DOR will be summarized descriptively for Groups A and B using the Kaplan-Meier method. For such subjects, the progression or censoring date will be determined based on described conventions (Food and Drug Administration, 2007).

Progression-free survival, median PFS, and the estimated rate at 6 months (PFS6) based on the Kaplan-Meier analyses will be reported separately for Groups A and B. For OS, the estimated rates at 3, 6, 9, and 12 months based on the Kaplan-Meier analyses will be reported for Groups A and B. For DOR, the estimate of the median based on the Kaplan-Meier analyses for Groups A and B will be reported.

Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of the product diameters in measurable nodes and nodal masses.

Secondary analyses of efficacy will be conducted based on the ITT and Evaluable Populations using response as determined by both the central determination of disease response and investigator site. In these analyses, the primary efficacy endpoint, ORR, will be estimated using the proportion of subjects with CR or PR. The estimate will be accompanied by a two-sided exact binomial 95% lower CB.

14.4.3.1. Interim Analyses

Interim analyses of efficacy using the Evaluable Population will be performed after ORR has been determined in 25 evaluable subjects for both Groups A and B, separately. In both Groups A and B, the ORR using the local determination of disease response will be obtained. If the lower bound of a single-sided 95% confidence interval using the exact binomial method is less than 10% (i.e., 5 responses or less out of 25 patients) in either group, enrollment in that group will not continue. Below are the 95% single-sided lower confidence intervals for various response rates using a sample size of 25 patients and employing the exact binomial methodology.

Sample Size	ORR	Lower 95% Single-Sided Confidence Bound
25	7 (28%)	14.0%
25	6 (24%)	11.0%
25	5 (20%)	8.2%[1]
25	4 (16%)	5.7%[1]

[1] Would result in stopping enrollment in that particular group(s).

14.4.4. Safety Analysis

The analyses of safety will be conducted based on the Safety Population. Analyses will be stratified by treatment. Safety will be assessed based on AEs, SAEs, laboratory values, vital signs, and ECG results.

Summary tables will be produced for all reported treatment-emergent AEs (TEAEs), defined as AEs that start or worsen on or after the first administration of study treatment. The reported AE term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be summarized based on the number and percentage of subjects experiencing the event by MedDRA system organ class and preferred term. The causal relationship between the occurrence of an AE and study treatment will be judged by the Investigator. In the event a subject experiences repeat episodes of the same AE, then the event with the highest severity grade and the event with the strongest causal relationship to study drug will be used for purposes of incidence tabulations.

Tabular summaries will be provided for:

- All TEAEs
- TEAEs by relationship to study treatment
- TEAEs by severity
- TEAEs occasioning treatment modification
- Serious TEAEs

All deaths that occur on study (defined as during treatment or within 30 days of treatment discontinuation) will be reported in a subject listing, which will include the primary cause of death and the number of days between the date of the last dose of study treatment and death. For subjects on combination treatment, the listing will show the date of last dose of each component.

Hematology and serum chemistries will be summarized using conventional summary statistics (mean, standard deviation, median, and range) for the following: baseline value, minimum and maximum post-baseline values, average post-baseline value, and last post-baseline value. Standard shift tables will also be prepared presenting worst post-baseline toxicity grade vs baseline. Vital signs and ECG results will be summarized in a descriptive manner by calculating

the mean, standard deviation, median, and range by time point in the same manner described for laboratory values.

Prior and concomitant medications will be coded to the generic term using the current version of the World Health Organization Drug Dictionary and will be tabulated by group and listed by subject.

14.4.5. Pharmacokinetic Analysis

Population PK analysis will be conducted to further understand the PK profile of CUDC-907 in patients with RR MYC-altered DLBCL. Linear mixed-effect modeling and/or a nonlinear mixed-effect modeling approach will be used in the study to better understand the PK profile of CUDC-907 in general Preliminary PK information has been collected during Phase 1, and the basic PK models of the drug have been established. In this study, blood samples will be obtained at 2 hours post-dose on Cycle 1 Day 1, Cycle 4 Day 1, and on Day 1 of every other cycle thereafter (i.e., Day 1 of Cycles 6, 8, 10, etc.). In addition, for the first 50 subjects enrolled on amendment 4, blood samples will also be obtained 2 hours post-dose on Days 8 and 15 of Cycle 1.

14.4.6. Multicenter Study

Data will be pooled across centers for all analyses.

14.4.7. Adjustments for Covariates

No adjustments for covariates will be made.

14.4.8. Missing Data

Unless otherwise stated, there will be no imputation of missing data, but dates for AEs and concomitant medications may be imputed conservatively if partial.

15. STUDY ADMINISTRATION

Regulatory authorities, the IRB/Independent Ethics Committee (IEC), and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

15.1. Case Report Forms and Source Documentation

For each subject, an eCRF and corresponding source records will be maintained at each clinical site. The eCRFs should be completed in a timely manner, and every effort should be made to have electronic forms completed and up-to-date in anticipation of a visit by the Sponsor's monitor.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertaining to the clinical study for each study participant.

All aspects of the study will be carefully monitored with respect to GCP and standard operating procedures for compliance with applicable government regulations. The study monitor will be an authorized individual designated by the Sponsor. The study monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the PI.

An electronic data capture system to manage data collection will be utilized during this trial. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. The system is fully compliant with Code of Federal Regulations 21 Part 11.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency.

A complete audit trail will be maintained of all data changes. The Investigator (or designee) will cooperate with the Sponsor (or its representative[s]) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

15.2. Investigator Documentation

Study staff will maintain appropriate medical and research records for this study, in compliance with International Conference on Harmonisation (ICH) E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

The Investigator will provide the Sponsor with a fully executed FDA Form 1572 including the Investigator's curriculum vitae. The Investigator will indicate on Form 1572 the name and

location of the clinical laboratory which will be used for subject evaluation. The laboratory's certification, certification number, and date of certification and the laboratory normal values will be provided. Any changes in the clinical laboratory or laboratory values will be provided promptly to the Sponsor who will report the changes to the FDA as required.

15.3. Record Retention

The Investigator will retain a copy of all study records in a secure location for a period of 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications OR until at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

15.4. Protocol Deviations and Amendment

The Investigator is not permitted to alter or deviate from the protocol without written agreement from the Sponsor. Any such agreement should be reported by the Investigator to their IRB/IEC. An immediate and unapproved deviation is permitted if immediate health care concerns mandate it.

All protocol revisions (amendments) must originate with and be documented by the Sponsor. The Investigator must submit the amendment to his/her IRB/IEC for review and approval prior to implementation. Documentation of approval signed by the chairperson or designee must be sent to the Sponsor.

15.5. Institutional Review Board/Independent Ethics Committee

The protocol, ICF(s), recruitment materials, and all patient materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled at any given investigative center, and a copy of the approval letter supplied to the Sponsor or Sponsor's designee. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented in the study.

During the course of the study, the Investigator shall make timely and accurate reports to the IRB/IEC on study progress at intervals not exceeding one year, as well as satisfying any other local IRB/IEC reporting regulations. Copies of all reports to, and correspondence with, the IRB/IEC must be provided to the Sponsor or Sponsor's designee. Further, within three months of the completion or early termination of the study, a final report should be made to the IRB/IEC and Sponsor by the Investigator.

It is the Investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review to Sponsor representatives as part of the routine study monitoring process.

15.6. Study Committees

A Safety Review Committee (SRC) comprised of the Medical Monitor, PI, and Sponsor representatives will be convened to review safety information for ongoing safety surveillance.

The SRC is tasked with making a recommendation to continue or stop the trial based on their assessment of available efficacy and safety information (see Section 9.3.2 for SRC stopping criteria).

15.7. Sponsor Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed in order to comply with GCP guidelines. After satisfactory receipt of all necessary regulatory paperwork, the Sponsor's monitor will arrange that all study material be delivered to the study site at a mutually convenient time. An initiation visit by the Sponsor and its monitoring personnel will be made. At this meeting, all personnel expected to be involved in the conduct of the study will undergo an orientation to include review of study protocol, instruction for eCRF completion and overall responsibilities, including those for drug accountability and study file maintenance.

Throughout the course of the study, the Sponsor's monitor will make frequent contact with the Investigator. This will include telephone and/or on-site visits. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. As part of the data audit, it is expected that source documents (e.g., hospital records, office records) will be made available for review by the monitor. The monitor also will perform drug accountability checks, and may periodically request review of the Investigator's study file to assure completeness of documentation in all respects of study conduct.

Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 15.3. The Investigator or appointed delegate will receive the Sponsor's representative during these on-site visits and will cooperate in providing the documents for inspection and responding to inquiries that may arise as part of this review. The Investigator will also permit inspection of the study files by authorized representatives of the FDA and regulatory authorities of other countries.

15.8. Publication/Data Sharing Policy

Publication by the sites of any data from this study must be in accordance with the clinical trial agreement.

16. ETHICS/PROTECTION OF HUMAN PATIENTS

16.1. Ethical Conduct of the Study

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH, GCP guidelines, applicable regulatory requirements, and Curis policies. The Investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Patients of Research, as drafted by the U.S. National Commission for the Protection of Human Patients of Biomedical and Behavioral Research (18 April 1979) and codified in 45 Code of Federal Regulations (CFR) Part 46 and/or the ICH E6.

16.2. Informed Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to patients and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the patient. Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator (or designee) will provide the Sponsor with a copy of the IRB-/IEC-approved ICF prior to the start of the study.

The ICF must be signed and dated; one copy will be given to the patient and the Investigator will retain a copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented. Patients will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained and documented from each patient prior to entry into the study. The consent process will be documented in the eCRF.

16.3. Confidentiality and Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, Investigator's Brochures, and other material) will be stored appropriately to ensure

their confidentiality. Patient data will be made available upon request to monitors from the Sponsor, the FDA, the Institutional Review Board, and to other government agencies that have responsibility for clinical research activities.

The anonymity of participating subjects must be maintained. Data that are released by the Investigator to the Sponsor, the FDA, or IRB/IEC will not be directly traceable to the patient. Documents that identify the patient (e.g., the signed informed consent document) must be maintained in confidence by the Investigator. In the event that a publication of this research incorporates a patient's medical data, that data will not identify the patient.

17. LIST OF REFERENCES

Akyurek N, Uner A, Benekli M, Barista I. Prognostic significance of MYC, BCL2, and BCL6 rearrangements in patients with diffuse large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab. Cancer. 2012 Sep 1;118(17):4173-83.

Asano T, Yao Y, Zhu J, Li D, Abbruzzese JL, Reddy SA. The PI 3-kinase/Akt signaling pathway is activated due to aberrant Pten expression and targets transcription factors NF-kappaB and c-Myc in pancreatic cancer cells. Oncogene. 2004 Nov;23(53):8571-80.

Barrans S, Crouch S, Smith A, Turner K, Owen R, Patmore R, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol. 2010 Jul 10;28(20):3360-5.

Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014 Sep 20;32(27):3048-58.

Bechard M, Dalton S. Subcellular localization of glycogen synthase kinase 3beta controls embryonic stem cell self-renewal. Mol Cell Biol. 2009 Apr;29(8):2092-104.

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013 Mar 1;132(5):1133-45.

Carbone PP, Kaplan H, Musshoff K, Smithers D, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971;Nov 31(11):1860-1861.

Carbone A, Gloghini A, Kwong YL, Younes A. Diffuse large B cell lymphoma: using pathologic and molecular biomarkers to define subgroups for novel therapy. Ann Hematol. 2014 Aug;93(8):1263-77.

Chambers AE, Banerjee S, Chaplin T, Dunne J, Debernardi S, Joel SP, et al. Histone acetylation-mediated regulation of genes in leukaemic cells. Eur J Cancer. 2003 May;39(8):1165-75.

Cheah CY, Oki Y, Westin JR, Turturro F. A clinician's guide to double hit lymphomas. Br J Haematol. 2015 Mar;168(6):784-95.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5):579-86.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphorra Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and

response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

Colosia A, Njue A, Trask PC, Olivares R, Khan S, Abbe A, et al. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review. Clin Lymphoma Myeloma Leuk. 2014 Oct;14(5):343-355.e6.

Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature. 1995 Dec 21-28;378(6559):785-9.

Cuccuini W, Briere J, Mounier N, Voelker HU, Rosenwald A, Sundstrom C, et al. MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. Blood. 2012 May 17;119(20):4619-24.

Duan H, Heckman CA, Boxer LM. Histone deacetylase inhibitors down-regulate bcl-2 expression and induce apoptosis in t(14;18) lymphomas. Mol Cell Biol. 2005 Mar;25(5):1608-19.

Food and Drug Administration/Center for Drug Evaluation and Research [Internet]. Guidance for industry. Clinical trial endpoints for the approval of cancer drugs and biologics. [Updated 2007; cited 2015 Oct 26]. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf

Friedberg JW, Fisher RI. Diffuse large B-cell lymphoma. Hematol Oncol Clin North Am. 2008 Oct;22(5):941-52.

Gandhi S. Diffuse large cell lymphoma. Medscape Drugs & Diseases [Internet]. 2014 Jan 6 [cited 2015 October 28]. Available from: http://emedicine.medscape.com/article/202969-overview#aw2aab6b2b5

Gisselbrecht G, Glass B, Laurent G, Gill DS, Linch MD, Trneny M, et al. Maintenance with rituximab after autologous stem cell transplantation in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL): CORAL final analysis. J Clin Oncol. 2011 May 20 Supplement;29(15):8004.

Green TM, Young KH, Visco C, Xu-Monette ZY, Orazi A, Go RS, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012 Oct 1;30(28):3460-7.

Gui CY, Ngo L, Xu WS, Richon VM, Marks PA. Histone deacetylase (HDAC) inhibitor activation of p21WAF1 involves changes in promoter-associated proteins, including HDAC1. Proc Natl Acad Sci U S A. 2004 Feb 3;101(5):1241-6.

Gupta M, Maurer MJ, Wellik LE, Law ME, Han JJ, Ozsan N, et al. Expression of Myc, but not pSTAT3, is an adverse prognostic factor for diffuse large B-cell lymphoma treated with epratuzumab/R-CHOP. Blood. 2012 Nov 22;120(22):4400-6.

Horn H, Ziepert M, Becher C, Barth TF, Bernd HW, Feller AC, et al; German High-Grade Non-Hodgkin Lymphoma Study Group. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. Blood. 2013 Mar 21;121(12):2253-63.

Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

Hu S, Xu-Monette ZY, Tzankov A, Green T, Wu L, Balasubramanyam A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. Blood. 2013 May 16; 121(20):4021-31.

Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012 Oct 1;30(28):3452–3.

Kenney AM, Widlund HR, Rowitch DH. Hedgehog and PI-3 kinase signaling converge on Nmyc1 to promote cell cycle progression in cerebellar neuronal precursors. Development. 2004 Jan;131(1):217-28.

Klapper W, Stoecklein H, Zeynalova S, Ott G, Kosari F, Rosenwald A, et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. Structural aberrations affecting the MYC locus indicate a poor prognosis independent of clinical risk factors in diffuse large B-cell lymphomas treated within randomized trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Leukemia. 2008 Dec;22(12):2226-9.

Kluk MJ, Chapuy B, Sinha P, Roy A, Dal Cin P, Neuberg DS, et al. Immunohistochemical detection of MYC-driven diffuse large B-cell lymphomas. PLoS One. 2012;7(4):e33813.

Kumar A, Marqués M, Carrera AC. Phosphoinositide 3-kinase activation in late G1 is required for c-Myc stabilization and S phase entry. Mol Cell Biol. 2006 Dec;26(23):9116-25.

Kurland JF, Tansey WP. Myc-mediated transcriptional repression by recruitment of histone deacetylase. Cancer Res. 2008 May 15;68(10):3624-9.

Li S, Weiss VL, Wang XJ, Desai PA, Hu S, Yin CC, et al. High-grade B-cell Lymphoma With MYC Rearrangement and Without BCL2 and BCL6 Rearrangements Is Associated With High P53 Expression and a Poor Prognosis. Am J Surg Pathol. 2016 Feb;40(2):253-61.

Liu T, Tee AE, Porro A, Dwarte T, Liu PY, Iraci N, et al. Activation of tissue transglutaminase transcription by histone deacetylase inhibition as a therapeutic approach for Myc oncogenesis. Proc Natl Acad Sci USA. 2007 Nov 20; 104(47):18682-7.

Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989 Nov 1;7(11):1630-6.

Macpherson N, Lesack D, Klasa R, Horsman D, Connors JM, Barnett M, et al. Small noncleaved, non-Burkitt's (Burkit-Like) lymphoma: cytogenetics predict outcome and reflect clinical presentation. J Clin Oncol. 1999 May;17(5):1558-67.

Miura K, Takahashi H, Nakagawa M, Izu A, Sugitani M, Kurita D, et al. Clinical significance of co-expression of MYC and BCL2 protein in aggressive B-cell lymphomas treated with a second line immunochemotherapy. Leuk Lymphoma. 2015 Oct 22:1-7.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-655.

Oki Y, Noorani M, Lin P, Davis RE, Neelapu SS, Ma L, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. Br J Haematol. 2014 Sep;166(6):891-901.

Perry AM, Alvarado-Bernal Y, Laurini JA, Smith LM, Slack GW, Tan KL, et al. MYC and BCL2 protein expression predicts survival in patients with diffuse large B-cell lymphoma treated with rituximab. Br J Haematol. 2014 May;165(3):382-91.

Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014 Oct 9;124(15):2354-61.

Pfeifer M, Grau M, Lenze D, Wenzel SS, Wolf A, Wollert-Wulf B, et al. PTEN loss defines a PI3K/AKT pathway-dependent germinal center subtype of diffuse large B-cell lymphoma. Proc Natl Acad Sci U S A. 2013 Jul 23;110(30):12420-5.

Polack A, Eick D, Koch E, Bornkamm GW. Truncation does not abrogate transcriptional downregulation of the c-myc gene by sodium butyrate in Burkitt's lymphoma cells. EMBO J. 1987 Oct;6(10):2959-64.

Qian C, Lai CJ, Bao R, Wang DG, Wang J, Xu GX, et al. Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. Clin Cancer Res. 2012 Aug 1;18(15):4104-13.

Savage KJ, Johnson NA, Ben-Neriah S, Connors JM, Sehn LH, Farinha P, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood. 2009 Oct 22;114(17):3533-7.

Scott DW, Mottok A, Ennishi D, Wright GW, Farinha P, Ben-Neriah S, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. J Clin Oncol. 2015 Sep 10;33(26):2848-56.

Sehn LH. Paramount prognostic factors that guide therapeutic strategies in diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2012;2012:402-9.

Swerdlow SH, Campo E, Harris NL, et al, eds.WHO classification of tumours of haematopoieticand lymphoid tissues. In: Bosman FT, Jaffe ES,Lakhani SR, Ohgaki H, eds. World Health Organization Classification of Tumours. Lyon,France: I ARC; 2008.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 May 19;127(20):2375-90

Thieblemont C, Briere J, Mounier N, Voelker HU, Cuccuini W, Hirchaud E, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy

in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol. 2011 Nov 1;29(31):4079-87.

Tzankov A, Xu-Monette ZY, Gerhard M, Visco C, Dirnhofer S, Gisin N, et al. Rearrangements of MYC gene facilitate risk stratification in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Mod Pathol. 2014 Jul;27(7):958-71.

Valera A, López-Guillermo A, Cardesa-Salzmann T, Climent F, González-Barca E, Mercadal S, et al; Grup per l'Estudi dels Limfomes de Catalunya i Balears (GELCAB). MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Haematologica. 2013 Oct;98(10):1554-62.

Visco C, Tzankov A, Xu-Monette ZY, Miranda RN, Tai YC, Li Y, et al. Patients with diffuse large B-cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC status: a report from an International DLBCL rituximab-CHOP Consortium Program Study. Haematologica. 2013 Feb;98(2):255-63.

Zhang X, Zhao X, Fiskus W, Lin J, Lwin T, Rao R, et al. Coordinated silencing of MYC-mediated miR-29 by HDAC3 and EZH2 as a therapeutic target of histone modification in aggressive B-Cell lymphomas. Cancer Cell. 2012;22(4):506-23.

Zhou K, Xu D, Cao Y, Wang J, Yang Y, Huang M. C-MYC aberrations as prognostic factors in diffuse large B-cell lymphoma: a meta-analysis of epidemiological studies. PLoS One. 2014 Apr 16;9(4):e95020.

APPENDIX A. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

ECOG Performance Status	
Grade	**Description**
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al, 1982

APPENDIX B. ANN ARBOR CLASSIFICATION

1. Stage According to Sites Involved by Lymphoma

Stage	Features
I	Involvement of a single lymph node region* or lymphoid structure
II	Involvement of two or more lymph node regions,* or localized involvement of one extranodal site and one or lymph node regions, all on the same side of the diaphragm
III	Involvement of lymph node regions* or structures on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, OR isolated extralymphatic organ involvement without adjacent regional lymph node involvement, but with disease in distant site(s), OR any involvement of the liver, bone marrow, pleura or CSF

* Lymph node regions include: right cervical (including cervical, supraclavicular, occipital, and preauricular lymph nodes), left cervical, right axillary, left axillary, right infraclavicular, left infraclavicular, mediastinal, hilar, periaortic, mesentery, right pelvic, left pelvic, right inguinal femoral, and left inguinal femoral

2. Relevant Suffixes

Suffix	Meaning
A	Absence of constitutional symptoms
B	Constitutional symptoms: fever (> 38°C), drenching sweats, weight loss (10% body weight over 6 months)
E	Involvement of a single, extranodal site contiguous or proximal to a known nodal site (stages I to III only; additional extranodal involvement is stage IV)
S	Splenic involvement
X	Bulky disease, defined as one or more site of disease of > 10 cm diameter, or mediastinal widening to > 1/3 of the chest width on chest X-ray

Other designations may include involved extranodal site(s): M = marrow, L = lung, H = liver, P = pleura, O = bone, D = skin and subcutaneous tissue; and the number of disease sites (e.g. II_2, II_4)

Source: Adapted from Carbone et al, 1971 and Lister et al, 1989

APPENDIX C. RECOMMENDATIONS FOR INITIAL EVALUATION, STAGING, AND RESPONSE ASSESSMENT OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE LUGANO CLASSIFICATION

Table 3. Revised Criteria for Response Assessment

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

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

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

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

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

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

Source: Cheson et al, 2014

APPENDIX D. ROLE OF IMAGING IN THE STAGING AND RESPONSE ASSESSMENT OF LYMPHOMA: CONSENSUS OF THE INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMAS IMAGING WORKING GROUP; 5-PS SCORE

The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

- 1. No uptake above background
- 2. Uptake < mediastinum
- 3. Uptake > mediastinum but < liver
- 4. Uptake moderately higher than liver
- 5. Uptake markedly higher than liver and/or new lesions
- X. New areas of uptake unlikely to be related to lymphoma

Source: Barrington et al, 2014

APPENDIX E. INTERNATIONAL PROGNOSTIC INDEX (IPI) CLASSIFICATION

One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH
- ECOG/Zubrod performance status of 2, 3, or 4
- More than 1 extranodal site

Source: The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993