A PHASE 1/2A OPEN-LABEL, MULTI-DOSE, MULTI-CENTER ESCALATION AND EXPLORATORY STUDY OF CERDULATINIB (PRT062070) IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL) OR B-CELL OR T-CELL NON-HODGKIN LYMPHOMA (NHL)

DRUG NAME: Cerdulatinib (PRT062070)

PROTOCOL NUMBER: 13-601

PHASE: 1/2a

IND NUMBER: 118394

EUDRACT NUMBER: 2016-002182-65

TRIAL SPONSOR: Portola Pharmaceuticals, Inc.
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South San Francisco, CA 94080
[redacted]

MEDICAL MONITORS: [redacted]
Portola Pharmaceuticals, Inc.
[redacted]
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PROTOCOL DATE:

Original:	14 August 2013
Amendment 1:	26 September 2013
Amendment 2:	19 November 2013
Amendment 3:	02 April 2015
Amendment 4:	06 April 2016
Amendment 5:	12 October 2016
Amendment 6:	05 May 2017
Amendment 7*:	06 March 2019
Amendment 8:	04 April 2019
Amendment 9:	14 October 2019

**Amendment 7 was superseded by Amendment 8 prior to distribution/operationalization.*

CONFIDENDIALITY STATEMENT

This protocol is the property of Portola Pharmaceuticals, Inc. It is a confidential communication. Acceptance implies an agreement not to disclose information contained herein that is not otherwise publicly available, with the exception that it may be disclosed to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the purpose of obtaining approval to conduct the study. The IRB/IEC is requested and expected to maintain confidentiality. This document may not be used or published without the consent of Portola Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for cerdulatinib. I have read Amendment 9 to Protocol number 13-601 entitled *A Phase 1/2A Open-Label, Multi-Dose, Multi-Center Escalation and Exploratory Study of Cerdulatinib (PRT062070) in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) OR B-Cell or T-Cell Non-Hodgkin Lymphoma*. I agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Investigator

Date

Printed Name of Investigator

SPONSOR'S AGREEMENT

I have read Amendment 9 to Protocol number 13-601 entitled *A Phase 112A Open-Label, Multi-Dose, Multi-Center Escalation and Exploratory Study of Cerdulatinib (PRT062070) in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) ORB-Cell or T-Cell Non-Hodgkin Lymphoma* and agree to abide by all provisions set forth therein.

I agree to comply with the ICH Tripartite Guideline on Good Clinical Practice (GCP), applicable Food and Drug Administration (FDA) regulations set forth in 21 CFR Parts 11, 50, 54, 56, 312 and all locally applicable laws.

[redacted]

10/14/19
Date (DD MMM YYYY)

Portola Pharmaceuticals, Inc.
South San Francisco, CA
USA

STUDY CONTACT INFORMATION AND PROCEDURES IN CASE OF EMERGENCY

Table 1: Study Contact Information and 24-Hour Emergency Contact

Role in Study	Name	Contact Information
Portola Responsible Physician/Medical Monitor	[redacted]	Portola Pharmaceuticals, Inc. 270 East Grand Avenue South San Francisco, CA 94080 Phone: [redacted] Email: [redacted]
Drug Safety Physician, Syneos Health Medical Monitor	[redacted]	Phone: [redacted] Email: [redacted]
24-Hour SAE Reporting Procedures	Not applicable	Report SAEs using the methods described on the SAE cover form, e.g., email to [redacted]
General Study Inquiries and Communication, Pre-screening Information, Enrollment Forms	Cerdulatinib Clinical Study Mailbox	[redacted]
IP Requests and Complaints	13601 Drug Mailbox	[redacted]
Lab Kit Requests and Lab Shipment Notifications	13601 Lab Mailbox	[redacted]

Table 2: Summary of Key Changes from Original Protocol (14 August 2013): Amendments 1 through 9

<table>
<tr><th>Protocol Version: Date</th><th colspan="2">Key Changes</th></tr>
<tr><td>Original:
14 August 2013</td><td colspan="2">• The original version of Protocol Number 13-601, a clinical study that investigated PRT062070 (hereafter referred to as “cerdulatinib”), was entitled A Phase I Open-Label, Multi-Dose, Dose-Escalation Study of PRT062070 in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) or B-Cell Non-Hodgkin Lymphoma (NHL).</td></tr>
<tr><td>Amendment 1:
26 September 2013</td><td colspan="2">Incorporated changes to the protocol as recommended by FDA in response to the Original Investigational New Drug (IND) Application 118394 for PRT062070, as follows:
• Changed starting dose from 15 mg BID to 15 mg QD.
• Clarified DLT criteria regarding the exclusion of patients for DLT evaluation and AEs leading to treatment discontinuation.
• Modified DLT hematologic criteria and made additional changes to DLT criteria.
• Added of CBC and serum chemistry testing on Days 1 and 15 for Cycles 2 through 4.</td></tr>
<tr><td>Amendment 2:
19 November 2013</td><td colspan="2">• Added additional PK monitoring during the first cycle. In order to do this the cycle length was changed from 21 days to 28 days throughout.
• Changed the schedule of tumor assessments from every 4 cycles after the first assessment at Cycle 3 to every 3 cycles. This maintained tumor assessments at every 12 weeks with the new cycle length of 28 days.
• Started QD dosing and allowed for flexibility to test BID dosing, depending on available PK data from prior cohorts.
• Added a list of strong CYP3A inhibitors and inducers and caution the Investigator as to their use.</td></tr>
<tr><td rowspan="4">Amendment 3:
02 April 2015</td><td colspan="2">• Changed the design of the study so as to conduct Part 2 (Dose Expansion phase) of the study using a 45 mg QD dose in 2 Groups of up to 40 patients each:
o Group 1 was planned for patients with CLL/SLL who had progressed or relapsed on prior therapy with any Bruton’s tyrosine kinase (BTK) inhibitor (such as ibrutinib) or any phosphatidylinositide 3 kinase (PI3K) inhibitor (such as idelalisib)
o Group 2 was planned for patients with FL who had progressed or relapsed on prior therapy.
• Substituted the name cerdulatinib for PRT062070 throughout the protocol. Note: The title of the study was not changed and still read A Phase I Open-Label, Multi-Dose, Dose Escalation.</td></tr>
<tr><td colspan="2">Study of PRT062070 in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) or B-Cell Non-Hodgkin Lymphoma (NHL)</td></tr>
<tr><td>1</td><td>Patients with FL Grade 1 to 3A/iNHL who have received ≥ 1 prior treatment regimen.</td></tr>
<tr><td>2</td><td>Patients with FL Grade 1 to 3A/iNHL who have received ≥ 1 prior treatment regimen. In addition to receiving cerdulatinib, this cohort will also receive rituximab IV at 375 mg/m2 during Cycle 1 on Days 1, 8, 15, and 22 of Cycle 1 and during Cycles 4, 6, 8, and 10 on Day 1 only.</td></tr>
</table>

Protocol Version: Date	Key Changes	
	3	Patients with aggressive NHL (aNHL), defined as DLBCL, FL 3B, MCL, and transformed NHL. These patients have relapsed from ≥ 1 but ≤ 3 prior cytotoxic chemotherapy regimens with an anti CD20 antibody, (e.g., R-CHOP, BR). Patients must have received an anthracycline based therapy unless anthracyclines were deemed inappropriate in the judgement of the investigator. Patients must have either relapsed following ASCT or not be candidates (ineligible) for ASCT, defined as meeting any of the following criteria [1]: a) age ≥ 70 years; b) DLCO < 50% by pulmonary function tests; c) FEV1/FVC < 60% predicted by pulmonary function tests; d) LVEF < 45% by MUGA or echocardiogram; e) uncontrolled arrhythmia; f) calculated creatinine clearance (Cockcroft-Gault) ≤ 60 mL/min; g) other comorbidities (e.g., medical conditions or psychosocial conditions) that would likely result in an unacceptably high probability of treatment/ transplant related morbidity and mortality in the judgement of the investigator (e.g., high HCT-CI, CIRS, scores); h) refusal of ASCT. (Note: Antibody drug conjugates (ADC) count as cytotoxic chemotherapy. Salvage chemotherapy prior to ASCT with or without maintenance therapy counts as one regimen.)
	4	Patients with CLL/SLL who have received ≥ 1 prior treatment regimen.
	5	Patients with PTCL NHL who have received ≥ 1 prior systemic treatment regimen for PTCL.
	6	Patients with CTCL NHL who have received ≥ 1 prior systemic treatment regimen for CTCL.
Amendment 4: 06 April 2016	• ***Changes to the study design:*** Updated the overall study design so that Protocol 13-601 was described as an open-label, Phase 1/2a, multi-dose, multi-center trial of orally administered cerdulatinib with 2 distinct phases (note that at the time of implementation of Amendment 4, the Phase 1 portion of the study is closed to enrollment). o Expanded Phase 2a (Exploratory) portion to include 6 cohorts, each defined by cancer type and prior therapy: • **Title Change:** Changed title of protocol to A Phase I/2a Open-Label, Multi-Dose, Multi-Center Escalation and Exploratory Study of Cerdulatinib (PTR062070) In Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) or B-Cell or T-Cell Non Hodgkin Lymphoma (NHL). • Updated/clarified Phase 2 objectives to address 6 cohorts. • Updated/clarified Phase 2 endpoints to address 6 cohorts. • Updated Phase 2a cancer-specific Inclusion Criteria. • Updated Exclusion Criteria to apply to patients in Phase 2a. • Updated the Statistical Analysis Plan to apply to Phase 2a. • Updated or added the following appendices: o Appendix 3, *Eastern Cooperative Oncology Group (ECOG) Performance Status*; Appendix 4, Table of Strong CYP3A4 Inhibitors and Inducers (and also added Table of CYP3A Sensitive Substrates); Appendix 5, added response definitions for B-cell NHL, PTCL, CLL, CTCL, and WM; Appendix 6, added prognostic indices for the following: Follicular Lymphoma International Prognostic Index-1 (FLIPI) Criteria, International Prognostic Index (IPI) Criteria, Age-adjusted International Prognostic Index, Simplified Mantle-Cell Prognostic Index (MIPI), International Prognostic Scoring System for Waldenström's Macroglobulinemia (IPSSWM); Appendix 7, added decision tree for differential of ABC vs. GCG type of DLCBL by ICH-Hans methodology; Appendix 8, added the following staging systems: Rai staging system for CLL, Binet staging system for CLL,	

Protocol Version: Date	Key Changes
Amendment 4: 06 April 2016 (Cont'd)	Lugano Modification of Ann Arbor staging system for nodal lymphoma; and Appendix 9, updated to clarify Global Health Assessment scale for patients to report their level of health and added that patients could decline to answer. • Established a Study Committee for Protocol 13-601.
Amendment 5: 14 Oct 2016	• Reduced starting dose of cerdulatinib from 35 mg BID to 30 mg BID, with subsequent reductions to 25 mg BID and then 20 mg BID permitted (Section 3.1.2.2.1 and throughout protocol). • Added pre- and post-study drug plasma sampling at C1D15 time point (Section 7.2.2.2). • Allowed unscheduled plasma samples for PK analyses to be collected at the discretion of the Investigator (e.g., in the event of an AE) (Section 9.1.2). • Added instruction to record date and time of last dose and last meal prior to PK sampling (Section 7.2.2.1 and throughout Section 7.2.2). • Modified Phase 2a General Inclusion Criteria, Section 4.1.2, item 5, to clarify the types of prior therapy allowed. • Modified Phase 2a General Inclusion Criteria, Section 4.1.2, item 7, to specify ANC and platelet criteria for CLL patients. • Modified Phase 2a General Inclusion Criteria, Section 4.1.2, item 8, to redefine adequate renal clearance. • Mandated prophylaxis for *Pneumocystis carinii* (PCP, aka *Pneumocystis jirovecii* Pneumonia) as well as prophylaxis for other opportunistic infections, per local standard of care or NCCN guidelines for all CLL enrolled patients; all other enrolled patients should receive prophylaxis described above (Section 7.6.2). • Identified AEs that may indicate potential drug toxicity (Section 10.1.3). • Updated routine chemistries to include assays for amylase and lipase (throughout Section 7.2.2 and Section 10.2.1). • Placed methodology applicable to the Phase 1 (Dose-Escalation) portion of the study (now closed to enrollment) in Appendix 12. • Added Table 2: Summary of Key Protocol Changes. • Made additional clarifications, deletions, and administrative corrections throughout the document and Appendices to improve clarity and consistency.
Amendment 6: 05 May 2017	• Dose reductions to 15 mg BID permitted (after reducing from 30 mg BID starting dose to 25 mg BID and then 20 mg BID) (Section 3.1.2.2.1) • Dose escalations permitted after a dose reduction (up to a maximum dose of 30 mg BID) at the discretion of the investigator based upon clinical judgement and with Sponsor Medical Monitor approval. • Modified Study Methods to remove visit-by-visit instructions and instead provide details on each assessment (Section 7.0). The visit-by-visit instructions can be found in Appendix 1. • Added the option for patients to have a reduced on-site visit cycle after Cycle 12 in the event of a treatment response at Investigator's discretion and with Sponsor Medical Monitor approval. The visit schedule can be reduced from on-site from Day 1 of every new cycle to every 3 cycles. Site staff should conduct phone visits for the cycles when the patient is not on-site (Section 7.3.2.1). • Clarified that patients should be on-site for Day 1 of all new cycles after Cycle 2 (Section 7.3.2). • Modified Inclusion Criteria, Section 4.1.2, item 8 to decrease minimum creatinine clearance from ≥ 60 mL/min to ≥ 50 mL/min and allow for urine collection to measure creatinine clearance.

Protocol Version: Date	Key Changes
Amendment 6: 05 May 2017 (Cont'd)	• Modified Exclusion Criteria, Section 4.2, item 11 to prohibit any active infection requiring systemic treatment (not limited to IV treatment). • Changed overdose reporting requirements, including specifying the timeframe to require reporting within 24 hours of awareness (Section 10.2.4.11). • Addition of DNA and MRD sampling time points (Appendix 1). • Reduced post-dose Vital Signs collection to only 1 hour post-dose for all cohorts except Cohort 2 (Section 7.1.6). • Clarified that bone marrow biopsy and aspiration should only be repeated as clinically indicated in patients who were marrow-positive for lymphoma at baseline and to verify response in CLL patients (Section 7.1.12.1). • Removed the criteria governing cohort expansion (Section 11.2.2). • Changed long-term survival follow-up from "a minimum of 2 years" to "up to 2 years" (Section 7.3.2.3). • Clarified that serum protein electrophoresis (SPEP) and serum immunoelectrophoresis (SIEP) are required for Cohort 1 WM patients (Appendix 1) • Removed 60 mg cerdulatinib formulation as well as 50-count bottle packaging (Section 6.1.1). • Added visit windows and visit guideline clarification based upon previous Global Memo #2 (Section 7.3.3 and Appendix 1). • Clarified that PPIs are a prohibited medication (Section 7.5.1). • Made additional clarifications, deletions, and administrative corrections throughout the document and Appendices to improve clarity and consistency.
Amendment 7: 06 March 2019	• Additional starting dose options were added for cerdulatinib. Starting doses are 30, 25, or 20 mg BID (Section 5.1.3). • Additional PK sampling was added at C1D1 and C1D8 at 1, 2, 4, 6, 8, and 24 hours post-dose, and the C1D15 post-dose sample was removed (Section 7.1.11). • Changes to Phase 2a general inclusion criteria (Section 4.1.2): o Prior therapy (IC #5) was updated to require patients with known CD30-expressing PTCL to have had at least one prior therapy that included a CD30-directed antibody (e.g., brentuximab vedotin). o Contraception requirements (IC #6) for Cohort 2 were aligned with the rituximab label, requiring patients use effective contraception during treatment with rituximab and for 12 months after the last dose of rituximab. o Adequacy of bone marrow reserves (IC #7) was updated to specify no limit on ANC or platelet count required for patients with leukemic forms of PTCL (ATLL, PLL, LGL) or hepatosplenic T-cell lymphoma (HSTCL). o Renal function inclusion (IC #8) was modified to require a creatinine clearance ≥ 30 mL/min (previously: serum creatinine level ≤ 2 upper limit of normal [ULN] and a creatinine clearance ≥ 50 mL/min). o Cohort 1 will no longer enroll patients with marginal zone lymphoma (MZL) or Waldenström's macroglobulinemia (IC #11). • Changes to Phase 2a exclusion criteria (Section 4.2): o Acid reducing agent (ARA) (EC #4) consumption was removed as an exclusion (e.g., ARAs are permitted), and it was clarified that intake of CYP3A4-sensitive substrates was also prohibited. o Prior therapy (EC #8) with alemtuzumab must have been greater than 3 weeks prior to C1D1 (previously: 8 weeks).

Protocol Version: Date	Key Changes
Amendment 7: 06 March 2019 (Cont'd)	○ HIV and hepatitis (EC #10): positive/negative status must be known, with additional testing required if a patient does not have documentation of prior negative hepatitis panel or negative HIV history for patients. ○ Removed the directive to administer cerdulatinib under fasting conditons; cerdulatinib may be administered with food (Section 5.1.1). ○ Peripheral blood quantitative EBV polymerase chain reaction assay (PCR) was added to the baseline assessment and should be performed post-baseline for any unexplained fevers if there is clinical suspicion of EBV reactivation (Section 5.2.1.4). ○ Guidance on the management of Grade 1 and 2 diarrhea, nausea and vomiting was added (Sections 5.2.1.5 and 5.2.1.6). ○ The guidelines for dose reductions for cerdulatinib were updated (Table 8). • Clarified that rituximab is not provided by the Sponsor as it is considered standard of care (Section 5.3). • Added collection of molecular/mutation profile if obtained as standard of care (Section 7.1.9.2). • Clarified that patients may continue adjuvant hormonal therapy for prostate or breast cancer (Section 7.5.1). • Immunosuppressive agents was removed as a prohibited medication group (Section 7.5.1). • Restrictions on the administration of anti-emetic agents were removed (Section 7.5.2). • Description of the Study Committee composition and function was revised to reflect current review practice (Section 7.6). • Assessement of Safety (Section 10.0) was revised for clarity. No new information was added. • For Cohort 1 iNHL patients only, whole blood sample collection for immune flow chemistry was removed from the protocol (Section 7.1.10.2 and Appendix 1). • Whole blood sample collection (all patients) for isolation of cell-free tumor DNA (ctDNA) was added (Section 7.1.10.1 and Appendix 1). • Post-dose vital signs assessments was removed from Cycle 2, Day 1 in the Schedule of Assessments (Appendix 1); a post-dose assessment was added in error to Cycle 2, Day 15. • Medical Monitor changed to [redacted] Syneos Health (previously: [redacted] Medical Monitor, INC Research). • Administrative Sections 12.0 – 16.0 were updated to align with company standard. • Appendix 12 was removed. This appendix contained the methodology applicable to the Phase 1 portion of the study which is closed, but may be referenced in earlier versions of the protocol.
Amendment 8: 04 April 2019	• Clarified instructions for the management of EBV reactivation (Section 5.2.1.4): in select cases, patients may continue to receive cerdulatinib with the Medical Monitor approval. • Clarified recording persistent versus recurrent adverse events (Section 10.2.4.3). • The Schedule of Assessments (Appendix 1) was updated for the following: a. Addition of a line item for HIV/HBV/HCV infection testing required as part of EC #10. b. Correction of pharmacodynamics sampling time point: removed at C1D9 and added at C1D8.

Protocol Version: Date	Key Changes
Amendment 9: 14 October 2019	• Updated this Summary of Key Changes table (Amendment 7) based on omissions identified and communicated in Global Study Memo #14. • Added an exception to the statement that any patients with a dose interruption of > 28 days should be permanently discontinued from cerdulatinib therapy (Section 5.2.1.3.1). • Updated Table 8 Guidelines for Dose Reductions for Cerdulatinib to state "may restart" instead of "restart" for consistency with language in Section 5.2.1.3.1 Dose Modifications to Cerdulatinib During Phase 2a. • Updated Section 5.2.1.5 Management of Diarrhea and Section 5.2.1.6 Management of Nausea and Vomiting to indicate that cerdulatinib can be restarted at the same dose level or at the next lower dose level. • Added details on new presentations of cerdulatinib that may be provided by Portola Pharmaceuticals, Inc. in Amendment 9 (Section 6.1.1). • Updated language in Section 7.1.6 Vital Signs for clarity and to allow post-dose vital sign measurements for Cohort 2 to be performed per standard of care. • Updated vital sign assessment window from ±5 minutes to ± 10 minutes in Section 7.1.6 Vital Signs for consistency with the Schedule of Assessments. • Deleted whole blood sample collection for pharmacodynamics and isolation of cell-free tumor DNA, as this is no longer needed (Section 7.1.10.1 and Schedule of Assessments [Appendix 1]) per Global Study Memo #15. • Deleted assessments for MRD (Sections 7.1.10.2, 7.1.12.2, 7.3.2.4, and 8.2.2; Schedule of Assessments [Appendix 1]) per Global Study Memo #15. • Updated Section 7.1.12.1 Bone Marrow Biopsy and Aspiration and the Schedule of Assessments (Appendix 1) for clarity and accuracy. • Removed the 2-year long-term follow-up from the study (Section 7.3.2.3; Schedule of Assessments [Appendix 1]), changed the definition of End of Study (Section 3.1.3) to reflect removal of the long-term follow-up, and changed the estimated study duration (Section 3.1.4; synopsis) to reflect removal of the long-term follow-up; removed references to long-term follow-up in Sections 5.2.1.3.1 and 5.2.1.3.2. • Updated language for flexibility in Section 7.6 Study Committee, since Principal Investigators may not be part of the Study Committee in Phase 2a. • Updated Section 3.1.5 Assessments, Section 9.2 Pharmacodynamic Assays, and Synopsis to accurately reflect sample collection. • Updated the causality categories and definitions of each category for adverse events (Section 10.2.3) • Updated the AE reporting term to "Disease Progression" for a death that is attributed solely to progression of the underlying malignancy (Section 10.2.4.7) to clearly distinguish between progression of an underlying malignancy (disease progression) and a new malignancy (new AE). • Corrected the rituximab infusion timepoints in the Schedule of Assessments (Appendix 1) for consistency with the protocol body and synopsis. • Deleted the post dose vital signs assessment at C2D15 in the Schedule of Assessments (Appendix 1) for consistency with the protocol body, as this was incorrectly added to the Schedule of Assessments in Amendment 7, but this assessment is not needed. • Added AE assessment at C1D9 and deleted AE assessment at long-term follow-up in the Schedule of Assessments in Appendix 1 (these were errors in Amendment 8).

SYNOPSIS

Name of Sponsor/Company: Portola Pharmaceuticals, Inc.

Name of Investigational Product: Cerdulatinib (PRT062070)

Name of Active Ingredient: Cerdulatinib (PRT062070)

Title: A Phase 1/2a Open-Label, Multi-Dose, Multi-Center Escalation and Exploratory Study of Cerdulatinib (PRT062070) in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) or B-Cell or T-Cell Non-Hodgkin Lymphoma (NHL)

Study Centers: Phase 1: 7 sites in the United States. Phase 2a: Approximately 40 sites in the United States.

Phase of Development: 1/2a

Study Duration: The duration of the study is approximately 6 years (Phase 1 and Phase 2a combined).

Objectives and Endpoints:

Phase 1 (Escalation portion)

Primary Objective

- To determine the maximum tolerated dose/maximum administered dose (MTD/MAD) of cerdulatinib in patients with relapsed/refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) or B-cell non Hodgkin lymphoma (NHL).

Secondary Objectives

- To make a preliminary assessment of the antitumor activity of cerdulatinib in patients with relapsed/refractory CLL/SLL or B-cell NHL, as assessed by overall response rate (ORR), defined as complete response (CR) + partial response (PR).
- To assess the safety and tolerability of cerdulatinib.
- To determine the pharmacokinetic (PK) profile of cerdulatinib.
- To evaluate the pharmacodynamics (PD) of cerdulatinib.

Phase 2a (Exploratory portion)

Primary Objective

- To assess the antitumor activity of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL, or CLL/SLL, as a single agent and in combination with rituximab for B-cell NHL.

Secondary Objectives

- To assess the duration of antitumor activity of cerdulatinib, amount of time to achieve tumor response, and magnitude of response.
- To further evaluate the PK profile of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL, alone or in combination with rituximab for B-cell NHL.
- To further evaluate the PD of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL, alone or in combination with rituximab for B-cell NHL.
- To assess tumor phenotype and genotype in relation to clinical response.
- To further evaluate the safety and tolerability of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL or CLL/SLL.
- To evaluate the safety and tolerability of the combination of cerdulatinib with rituximab for B-cell NHL.

Exploratory Objectives

- To evaluate the relationship between markers of inflammation with clinical outcome and overall health as determined by the Global Health Assessment.
- To assess Minimal Residual Disease (MRD) status in CLL patients achieving a complete response/complete response incomplete blood count recovery/partial response (CR/CRi/PR) by flow cytometry. MRD negativity (MRD-) is defined as < 1 CLL cell in 10,000 leucocytes. MRD+ (MR positivity) is defined as ≥ 1 CLL cell in 10,000 leucocytes.

Design and Methodology: This is an open-label, Phase 1/2a, multi-dose, multi-center trial of orally administered cerdulatinib with 2 phases:

- Phase 1 (closed to enrollment): Dose-escalation, during which patients will receive single-agent cerdulatinib at their assigned dose level.
  - Patients will have histologically confirmed diagnosis of CLL/SLL or B-cell non-Hodgkin lymphoma. In addition, they will meet all other eligibility criteria as specified in Section 4.0 and applicable subsections.
  - The starting dose of cerdulatinib will be 15 mg once daily (15 mg QD).
  - Cerdulatinib will be administered in increasing dose levels until the MTD/MAD is identified (see definitions, Table 3). If the MTD is not achieved, the highest studied dose will be declared the MAD and become the recommended Phase 2 dose (RP2D).
  - To allow for a single-dose PK assessment, patients on a QD regimen will take their first dose of cerdulatinib on Day 1 and their second and subsequent doses daily beginning on Day 4. Patients will receive cerdulatinib once daily for a total of 28 days (one cycle) to assess the MTD/MAD, except on Days 2 and 3, when they will not take cerdulatinib. Patients in twice daily (BID) dosing regimens will start cerdulatinib on Day 1 and will not skip any days.
  - One patient will be enrolled in each dose cohort until the first report of a Grade 2 or greater adverse event (AE).
    - In the event of any Grade 2 or greater AE in a single patient, an additional 2 patients, for a total of 3, will be enrolled in that dose cohort, and all subsequent dose cohorts will follow a "3 + 3" design.
    - Dose escalation will be in 100% increments until a drug-related AE of Grade ≥ 2 occurs. Thereafter, dose escalation will be in increments of up to 50% as determined following review by the Study Committee.
    - If a dose-limiting toxicity (DLT) occurs in 1 of the first 3 patients in a cohort, that cohort will be expanded to at least 6 patients.
      - If ≤ 33% of 6 or more patients in a cohort experiences DLT, dose escalation may proceed.
      - If in any cohort 2 or more of the first 3 patients or ≥ 33% of patients in a cohort develop DLT, dose escalation will cease, and that dose level will be declared intolerable. The prior dose level will either be declared the MTD, and the cohort may be expanded to as many as 6 patients if fewer than 6 patients had been treated previously at that dose level in order to further characterize the PK and PD at that level.
- The study is currently in Phase 2a: Exploratory, consisting of 6 cohorts, each defined by cancer type and prior therapy
  - Under Amendment 7, the starting dose of orally administered cerdulatinib is either 30, 25, or 20 mg BID. Subsequent de-escalations to 25, 20, and then 15 mg BID are permitted. A patient who has been de-escalated may be re-escalated at the discretion of the Investigator based upon clinical judgement and with Sponsor Medical Monitor approval per the Dose Modification Guidelines for Phase 2a (Section 5.2.1.3).
  - The 6 cohorts are defined below:
    - **Cohort 1**: Patients with follicular lymphoma Grade 1 to 3A who have received ≥ 1 prior treatment regimen.
    - **Cohort 2**: Patients with FL Grade 1 to 3A who have received ≥ 1 prior treatment regimen. In addition to receiving cerdulatinib, this cohort will also receive rituximab IV at 375 mg/m^2 during Cycle 1 on Days 1, 8, 15, and 22 and during Cycles 4, 6, 8, and 10 on Day 1 only.

- **Cohort 3**: Patients with aggressive NHL (aNHL), defined as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma Grade B (FL 3B), Mantle Cell lymphoma (MCL), and transformed NHL. These patients have relapsed from ≥ 1 but ≤ 3 prior cytotoxic chemotherapy regimens with an anti CD20 antibody, (e.g., R-CHOP, BR). Patients must have either relapsed following autologous stem cell therapy (ASCT) or not be candidates (ineligible) for ASCT, defined as meeting any of the following criteria [1]: a) age ≥ 70 years; b) DLCO < 50% by pulmonary function tests; c) forced expiratory volume in 1 second/forced vital capacity; (FEV_1/FVC) < 60% predicted by pulmonary function tests; d) left ventricular ejection fraction (LVEF) < 45% by multiple gated acquisition (MUGA) or echocardiogram; e) uncontrolled arrhythmia, f) calculated creatinine clearance (Cockcroft-Gault) ≤ 60 mL/min; g) other comorbidities (e.g., medical conditions or psychosocial conditions) that would likely result in an unacceptably high probability of treatment/transplant related morbidity and mortality in the judgement of the investigator (e.g., high Hematopoietic Cell Transplantation Co-Morbidity Index (HCT-CI), Cumulative Illness Rating Scale (CIRS) scores); h) refusal of ASCT.

  (Note: Antibody drug conjugates (ADC) count as cytotoxic chemotherapy. Salvage chemotherapy prior to ASCT with or without maintenance therapy counts as one regimen.)
- **Cohort 4**: Patients with CLL/SLL who have received ≥ 1 prior treatment regimen.
- **Cohort 5**: Patients with peripheral T-cell lymphoma (PTCL) NHL who have received ≥ 1 prior systemic treatment regimen for PTCL. In patients with CD30-expressing PTCL, prior treatment must include a CD30-directed antibody (e.g., brentuximab vedotin).
- **Cohort 6**: Patients with cutaneous T-cell lymphoma (CTCL) NHL who have received ≥ 1 prior systemic treatment regimen for CTCL.

Number of Patients (Planned):

Phase 1:	43 patients were enrolled and dosed. Enrollment to Phase 1 is closed.
Phase 2a:	Approximately 240 patients.
Total:	Up to 283 patients dosed for the entire study

Diagnosis and Main Criteria for Inclusion:

Phase 1 Cancer-Specific Inclusion Criteria

1. Patient must have a histologically confirmed diagnosis of 1 of the following:
   - CLL/SLL
   - B-cell non-Hodgkin lymphoma, any of the types specified below, all with relapsed or refractory disease:
     - Diffuse Large B-cell lymphoma (DLBCL)
     - Follicular lymphoma (FL)
     - Mantle cell lymphoma (MCL)
     - Mucosa Associated Lymphoid Tumor (MALT)
     - Marginal zone lymphoma (MZL)
     - Lymphoplasmacytic lymphoma (LPL)

Phase 1 General Inclusion Criteria

1. Patient has failed at least 1 prior established treatment regimen (e.g., progressed during, or refractory to), and no other standard therapy exists for that patient, or patient is intolerant of existing standard therapy or is not a candidate for such standard therapy.
2. Patient must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 or 1.
3. Patient must be 18 years or older, of either sex, and of any race.
4. Patient (and/or parent/guardian for patients who otherwise are unable to provide independent consent) must be willing to give written informed consent and be able to adhere to dose and visit schedules.

5. Female patients of childbearing potential and male patients must agree to abstain from sexual intercourse or to use an effective method of contraception during the study and for 90 days following the last dose of protocol therapy (examples of effective methods of contraception include oral contraceptives or double barrier methods such as condom plus spermicide or condom plus diaphragm).
6. Patient must have adequate bone marrow reserve as evidenced by an absolute neutrophil count (ANC) ≥ 1,000/µL AND platelet count ≥ 75,000/µL.
7. Patient must have adequate renal function as evidenced by a serum creatinine level ≤ 1.5 × upper limit of normal (ULN) or a calculated creatinine clearance > 60 mL/min.
8. Patient must have adequate hepatic function as evidenced by a serum bilirubin level ≤ 2.0 mg/dL AND serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels ≤ 2.5 × the ULN for the reference laboratory. Serum bilirubin must be ≤ 2.5 mg/dL when increase is clearly documented as due to Gilbert's syndrome.

Phase 2a Cancer-Specific Inclusion Criteria

Patient must have a histologically confirmed diagnosis of 1 of the following:

Note: Definitions for "relapsed" and "refractory" disease are provided in Table 3.

- FL Grade 1 to 3A, with relapsed or refractory disease.
- Aggressive NHL (aNHL), defined as DLBCL, FL Grade 3B, MCL, and transformed NHL with relapsed disease.
- CLL/SLL, with relapsed or refractory disease.
- PTCL, with relapsed or refractory disease.
- CTCL with relapsed or refractory disease. Only CTCL patients with MF/SS are allowed.

Patients who received any BCR pathway inhibitor (e.g., BTK inhibitors such as ibrutinib, or PI3 Kinase inhibitors such as idelalisib) and/or BCL2 pathway inhibitors (e.g., venetoclax), and were either intolerant to therapy or had relapsed/refractory disease following therapy are also eligible.

Phase 2a General Inclusion Criteria

1. Patient must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 or 1.
2. Patient must be 18 years or older, of either sex, and of any race.
3. Patient (and/or parent/guardian for patients who otherwise are unable to provide independent consent) must be willing to give written informed consent and be able to adhere to dose and visit schedules.
4. Patient has had prior treatment for lymphoid malignancy requiring treatment for progressive disease/refractory disease (per guidelines for diagnosis and treatment of CLL [2] and revised response criteria for malignant lymphoma [3]).
5. Patient has had ≥ 1 prior systemic treatment regimen administered for at least 2 cycles (unless the patient was intolerant or experienced documented progression on therapy) that must have involved either: (1) an anti-CD20 agent (such as rituximab) WITH chemotherapy for B-cell NHL, unless contraindicated in the judgement of the investigator (e.g., the patient was not a candidate for chemotherapy and received ibrutinib as firstline treatment); (2) a cytotoxic chemotherapy drug for T-cell NHL; (3) an anti-CD20 agent (such as rituximab) with chemotherapy for CLL, unless contraindicated in the judgement of the investigator (e.g., the patient was not a candidate for chemotherapy and received ibrutinib as firstline treatment); or (4) in patients with CD30-expressing PTCL, a CD30-directed antibody (e.g., brentuximab vedotin).
6. Female patients of childbearing potential and male patients must agree to abstain from sexual intercourse or to use an effective method of contraception during the study and for 90 days following the last dose of protocol therapy (examples of effective methods of contraception include oral contraceptives or double barrier methods such as condom plus spermicide or condom plus diaphragm). Patients enrolled into Cohort 2 should use effective contraception during treatment with rituximab and for 12 months after the last dose of rituximab.

7. Patient must have adequate bone marrow reserve as evidenced by an absolute neutrophil count (ANC) ≥ 1,000/µL, platelet count ≥ 75,000/µL. Platelet count must be without transfusion support within 7 days of the first dose of cerdulatinib.
   Note: CLL patients only: ANC ≥ 750/µL and platelet count ≥ 30,000/µL are acceptable. There are no limits on ANC or platelet count required for patients with leukemic forms of PTCL (ATLL, PLL, LGL) or hepatosplenic T-cell lymphoma (HSTCL) as long as cytopenia, if present, is secondary to disease.
8. Patient must have adequate renal function as evidenced by a creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault equation or based on a 24-hour urine specimen).
9. Patient must have adequate hepatic function as evidenced by a serum bilirubin level ≤ 2.0 mg/dL AND serum AST/ALT levels ≤ 2.5× the ULN for the reference lab. Serum bilirubin ≤ 2.5 mg/dL when increase clearly documented as due to Gilbert's syndrome.
10. Where available, ability to submit a formalin-fixed paraffin embedded tissue (FFPE) block or a minimum of 10 unstained, freshly cut FFPE tissue slides from lymph node or other biopsies that were collected as part of patient diagnosis. If samples are unavailable the patient is still eligible for enrollment.
11. Measureable disease for a given tumor type, defined as:
    a. The presence of ≥ 1 lesion that measures ≥ 1.5 cm in a single dimension as assessed by CT, CT/PET for patients with nodal or mass lesions (e.g., FL, DLBCL, other NHL), or
    b. Quantifiable circulating tumor cells for patients with circulating tumor (e.g., Sézary Syndrome [SS]), or
    c. For CTCL: mSWAT score > 0.
12. Ability to provide redacted copies of pathology reports and radiology reports used for the diagnosis of NHL or CLL. In addition, for CTCL, ability to provide redacted photographs of skin responses.

Phase 2a Cohort-Specific Inclusion Criteria

- Cohort 1 (FL): Grades 1 to 3A (Single-Agent Cerdulatinib): Received ≥ 1 prior treatment regimen.
- Cohort 2 (Combination): FL, Grades 1 to 3A (Cerdulatinib + Rituximab): Received ≥ 1 prior treatment regimen.
- Cohort 3 (aNHL): aNHL (Single-Agent Cerdulatinib): Aggressive non-Hodgkin lymphoma (aNHL) is defined as DLBCL, FL Grade 3B, Mantle Cell Lymphoma (MCL), and transformed NHL. Patients had relapsed from ≥ 1 but ≤ 3 prior cytotoxic chemotherapy regimens with an anti CD20 antibody, (e.g., R-CHOP, BR). Patients must have received an anthracycline based therapy unless anthracyclines were deemed inappropriate in the judgement of the investigator. Patients must have either relapsed following autologous stem cell therapy (ASCT), or not be candidates (ineligible) for ASCT, defined as meeting any of the following criteria [1]: a) Age ≥ 70 years; b) DLCO < 50% by pulmonary function tests; c) FEV_1/FVC < 60% predicted by pulmonary function tests; d) LVEF < 45% by MUGA or echocardiogram; e) uncontrolled arrhythmia; f) calculated creatinine clearance (Cockcroft-Gault) ≤ 60 mL/min; g) other comorbidities (e.g., medical conditions or psychosocial conditions) that would likely result in an unacceptably high probability of treatment/transplant related morbidity and mortality in the judgement of the investigator (e.g., high HCT-CI, CIRS, scores); h) Refusal of ASCT.
- Note: Antibody drug conjugates (ADC) count as cytotoxic chemotherapy. Salvage chemotherapy prior to ASCT with or without maintenance therapy counts as one regimen.
- Cohort 4 (CLL/SLL): CLL/SLL (Single-Agent Cerdulatinib): Received ≥ 1 prior treatment regimen.
- Cohort 5 (PTCL NHL): Peripheral T-cell NHL (PTCL) (Single-Agent Cerdulatinib): Received ≥ 1 prior systemic treatment regimen for PTCL. In patients with CD30-expressing PTCL, prior treatment must include a CD30-directed antibody (e.g., brentuximab vedotin).
- Cohort 6 (CTCL NHL): Cutaneous T-cell NHL (CTCL, MF/SS only) (Single-Agent Cerdulatinib): Received ≥ 1 prior systemic treatment regimen for CTCL.

Phase 1 and Phase 2a Exclusion Criteria

A patient meeting any 1 of the Exclusion Criteria listed below will be excluded from the trial, whether enrolled in Phase 1 or Phase 2a of the study.

1. Patient has Richter's syndrome, Burkitt's lymphoma, or Burkitt-like Lymphoma. Patients with transformed DLBCL from Follicular NHL are eligible.
2. Patient has undergone prior allogeneic or autologous transplant with infusion of stem cells within 90 days before Cycle 1 Day 1 (C1D1), or on active immunosuppressive therapy for graft-versus-host disease (GVHD) or GVHD prophylaxis within 8 weeks before C1D1.
3. Patient has received prior therapy with a spleen tyrosine kinase (SYK) inhibitor.
4. Patient requires chronic treatment with a strong CYP3A4 inhibitor or inducer or CYP3A4-sensitive substrate (Appendix 3).
5. Patient has known lymphomatous involvement of the central nervous system (CNS).
6. Patient has a known hypersensitivity to any of the components of cerdulatinib.
7. Patient has persistent, unresolved NCI CTCAE v5.0 ≥ Grade 2 clinically significant (in the judgement of the investigator) drug-related toxicity (except alopecia, erectile impotence, hot flashes, libido, neuropathy) associated with previous treatment.
8. Prior monoclonal antibody (Mab) (including alemtuzumab), radioimmunoconjugate, antibody drug conjugate (ADC), phototherapy, radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 3 weeks before Cycle 1 Day 1.
9. For CTCL patients only: total skin electron beam therapy (TSEBT) within 12 weeks, or initiation of topical steroid, nitrogen mustard, or topical retinoid within 2 weeks before Cycle 1 Day 1. Patients with CTCL who are on a stable topical regimen for ≥ 4 weeks prior to C1D1 are allowed.
10. The patient has a known infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) or is a carrier of HBV or HCV. Patients who are seropositive for HCV antibody must test negative for HCV by polymerase chain reaction (PCR) assay to be eligible. Patients with an occult or prior HBV infection (defined as being seropositive for total hepatitis B core antibody [HBcAb] and seronegative for HBsAg) may be included if his or her HBV DNA is undetectable or if it is undetectable with antiviral therapy. These patients must be willing to undergo additional testing per local standard of care if this data is unavailable. Additional testing will be performed if the patient does not have documentation of a negative hepatitis panel and negative HIV history within the 12-week period prior to enrollment.
11. Patient has an active infection requiring systemic treatment, defined as requiring antimicrobial, antifungal, or antiviral agents. Prophylactic antimicrobial treatment is permitted.
12. Patient has significant gastrointestinal disease that may interfere with absorption of the study drug or that predisposes him/her to GI adverse effects, or has had major gastric or bowel surgery.
13. Patient has difficulty swallowing or malabsorption syndrome.
14. Patient has any other medical, social, or psychiatric condition that might interfere with the patient's participation in the trial or interfere with the interpretation of trial results.
15. Patient has undergone major surgery within 4 weeks prior to first study drug administration.
16. Patient has a history (within 2 years prior to first study drug administration) of another malignancy unless malignancy treated with curative intent and likelihood of relapse is small (< 5% in 2 years in the judgement of the investigator). Patients with a history of squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix may be enrolled.
17. Patient is receiving systemic steroids at doses greater than the equivalent of prednisone, 20 mg daily, with the exception of intermittent use for the treatment of emesis.
18. Patient is female and is breast-feeding, pregnant, or intends to become pregnant.
19. Patient is participating in any other therapeutic clinical study (observational or registry trials are allowed).

Investigational Product, Dosage and Mode of Administration:

Cerdulatinib, administered orally (po) during both phases:

- Phase 1 (dose-escalation): Starting dose is 15 mg QD in increasing dose levels until the MTD/MAD is identified.
- Phase 2a (exploratory): Six cohorts are planned. Five cohorts will receive single-agent cerdulatinib and 1 cohort will receive cerdulatinib plus rituximab IV at 375 mg/m^2 during Cycle 1 on Days 1, 8, 15, and 22 and during Cycles 4, 6, 8, and 10 on Day 1 only.
- Cerdulatinib will be administered at the following starting dose levels: 30, 25, or 20 mg BID.

Duration of Treatment for Individual Patients and Duration of Study:

Patients enrolled under Phase 1 and Phase 2a portions of this study may continue to receive cerdulatinib in the absence of disease progression or intolerable toxicity or until they meet any other withdrawal criteria (Section 4.4). The total duration of the study (Phase 1 and Phase 2a) is expected to be ~6 years.

Reference Therapy, Dosage, and Mode of Administration: None.

Criteria for Evaluation:

Efficacy (Primary and Secondary)

Response Criteria: Response in NHL patients will be evaluated using The Lugano Classification [4]; in CLL patients using the Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia [2]; and in CTCL patients using the modified Severity Weighted Assessment Tool (mSWAT) and other measures as appropriate [5]. Appendix 4 provides definitions and detailed descriptions of response criteria as well as guidance on selection of lesions for evaluation. Redacted copies of radiology reports will be sent to the Sponsor for review.

Tumor/Lymph Node Biopsies: If tumor or lymph node or skin biopsies (including CTCL patients) biopsies are obtained during the course of the patient's treatment, redacted copies of the pathology reports should be sent to the Sponsor for review. In addition, a portion of the tumor block or at a minimum of 10 unstained slides should be sent for review as discussed in earlier sections of the protocol.

Exploratory Efficacy: Global Health Questionnaire and detection of minimal residual disease in CLL patients achieving a CR or CRi or PR using 4-color flow cytometry. MRD negativity (MRD-) is defined as < 1 CLL cell in 10,000 leucocytes. MRD positivity (MRD+) is defined as ≥ 1 CLL cell in 10,000 leucocytes.

Pharmacokinetic Assessments: *Phase 1:* Blood samples will be obtained at frequent intervals for determination of cerdulatinib concentration. Parameters calculated for all patients will be: plasma half-life ($t_{½}$); time to maximum observed plasma concentration (T_{max}); maximum observed plasma concentration (C_{max}); minimum observed plasma concentration (C_{min}); area under the plasma concentration-time curve from 0 to last measurable concentration ($AUC_{0\text{-}last}$) computed using the linear trapezoidal rule; total area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$); clearance of cerdulatinib (CL/F); volume of distribution of cerdulatinib at steady state (Vss/F); amount of drug excreted in urine over the sampling interval (Ae) for those patients for whom total volume of urine was collected; accumulation ratio, calculated by $AUC_{0\text{-}12}$ at steady-state/$AUC_{0\text{-}12}$ following the first dose for those patients for whom the 12-hour sample was collected.

Phase 2a: In order to further characterize the PK of cerdulatinib (specifically, C_{min}), serial plasma PK samples will be collected on Cycle 1 Days 1 and 8 at pre-dose and 1, 2, 4, 6, 8, and 24 hours post-dose. PK samples will also be taken pre-dose at Cycle 1 Day 15, Cycle 2 Day 1, and prior to Cycles 3, 6, 9, and every 3 cycles thereafter (to correspond with tumor assessment). Additional unscheduled PK plasma samples may be taken at the discretion of the Investigator (e.g., in the event of an AE or dose change).

Pharmacodynamic Assessments: Serum will be obtained at various time points throughout the trial to determine the effects of cerdulatinib on markers of inflammation. DNA and RNA (DNA only for Phase 2a) will be isolated from optional tumor biopsy specimens to assess genetic mutations relevant to the disease and the mechanism of action of cerdulatinib. The following will be assessed: quantification of serum proteins, quantitative polymerase chain reaction (PCR) for tumor relevant transcripts; hybridization of RNA to gene arrays, and DNA sequencing to identify disease-relevant mutations.

Safety: Safety will be monitored by serial physical exams, vital signs, hematology and chemistry laboratory studies, concomitant medications, and reported AEs (including deaths and other serious adverse events [SAEs] and treatment-related AEs).

Study Committee: Select study participants will comprise the Study Committee (e.g., selected Principal Investigators, Portola's Medical Monitor, Clinical Study Manager, and Drug Safety Medical Monitor). Other Portola or outside personnel may be called or consulted as needed. The Study Committee composition and functions are fully defined in Section 7.6. During Phase 1, the Study Committee will meet after all patients in any cohort have completed Cycle 1 to determine whether it is safe to escalate to the next dose of cerdulatinib or whether the MTD/MAD dose has been reached. If it is safe to continue, the committee will determine the next dose level to be studied. During Phase 2a, the Study Committee will meet periodically to review available safety and efficacy data from the study. Following the first meeting of the Study Committee, subsequent meetings will be held periodically as needed. Data to be evaluated may include (but are not limited to): deaths, other SAEs, AEs, including treatment-related AEs; reasons for treatment discontinuation or dose modification/interruption, trends in laboratory evaluations, and efficacy. For the combination cohort with rituximab, the Study Committee will evaluate (using the assessments as outline above) the first 3 to 6 patients who have completed Cycle 1 before allowing further enrollment in the cohort. Afterwards, the cohort can be evaluated with the rest of the other cohorts as above.

Statistical Methods:

General Considerations: Statistical summaries are expected to be performed using SAS software Version 9.3 (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used for the production of graphics.

Analysis Populations: The safety analysis population will consist of all patients treated with at least 1 dose of study medication (cerdulatinib). Safety data will be summarized by dose level, based on the original assigned dose of study drug. The efficacy analysis population for the primary and secondary efficacy endpoints will consist of all patients who have taken at least 1 dose of study medication and have had at least 1 post-baseline tumor assessment. Efficacy will be summarized separately for Phase 1 and 2a, and within Phase 2a will be summarized by cohort and dose level. The PK and PD analysis populations will consist of all patients who have received the requisite treatments and have data at the required time points. In order to determine cohort comparability, baseline and demographic characteristics of the Phase 1 and 2a cohorts will be summarized by dose cohort and overall. No formal analyses of these data are planned, but descriptive statistics may be used to aid in interpreting results.

Analysis of Efficacy Endpoints: Responses will be classified as complete response (CR), partial response (PR), stable disease (SD), disease progression (PD), or not evaluable. The overall response rate (ORR, defined as CR+PR) and clinical benefit rate (CR+PR+SD) will be summarized along with two-sided exact 95% confidence intervals. Responses will be based on computed tomography (CT) or computed tomography/positron emission tomography (CT/PET), evaluated per revised IWG Criteria [3] for patients with lymphoma and on peripheral lymphocyte counts and bone marrow biopsy results for patients with CLL [2]. Listings of tumor response for each patient will also be provided. Responses will be summarized separately for each dose level in Phase 1 and for each cohort and dose level in Phase 2a. Due to differences in underlying disease and prior treatment, response rates considered clinically significant and that would prompt further study will depend on the cohort. Such summaries will also depend on the safety and tolerability profile observed. While it is anticipated that a 30 to 40% response rate will be sufficient to support further investigation, no criteria for success in this study are specified.

In addition to the tumor response rates described above, the following efficacy endpoints will be assessed: duration of response (DOR), progression-free survival (PFS), lymph node response (LNR), and time-to-treatment response (TTR) (see definitions in Table 3).

Exploratory Efficacy – Phase 2a Only

As an exploratory assessment, patients will be asked to complete a Global Health Assessment (Appendix 8) to assess whether patients feel their overall health is improving on this study. The correlation between markers of inflammation with clinical response and the overall health (Global Health Assessment) will be assessed.

An additional exploratory assessment, detection of minimal residual disease (MRD) in CLL patients achieving a CR or CRi or PR will also be performed using at least 4 color flow cytometry by either local lab or a designated central lab in blood and/or marrow. MRD- (MRD negativity) defined as < 1 CLL cell in 10,000 leucocytes. MRD+ (MRD positivity) is defined as ≥ 1 CLL cell in 10,000 leucocytes.

Pharmacokinetic Analyses: PK parameters will be calculated for each patient for which adequate samples are available and summarized.

Pharmacodynamic Analyses, Phase 1 and 2a: A number of PD parameters (described above) will be measured serially. At each time point, each of these parameters will be summarized by dose level. In addition, the parameters over time will be plotted for each patient and dose cohort. No formal statistical analyses are planned.

Safety, Phase 1 and 2a: For the Phase 1 portion of the study, the primary safety endpoint is the incidence of DLT by dose level and the secondary safety endpoints are the AE profile (classified by NCI-CTCAE v5.0), clinically significant changes in vital signs and physical exams by dose level, and changes in hematology and chemistry laboratory parameters by dose level. The incidence of DLT will be summarized and listed by dose cohort for Phase 1.

For the Phase 1 and Phase 2a portions of the study, AEs will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v5.0 and coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the time of database creation. The number and percent of patients with any AE will be presented by System Organ Class (SOC) and preferred term for each cohort will be summarized by dose cohort for Phase 1 and by Cohort for Phase 2a. An additional summary will include all patients who received the dose used in Phase 2a. Vital signs, laboratory parameters, and ECG intervals will be summarized and listed by time point for each dose cohort for Phase 1 and by cohort for Phase 2a. No formal statistical analyses are planned.

Sample Size Considerations

Phase 1: The sample size is based on clinical judgment and is typical of studies of this type. A total of approximately 40 to 50 patients will be studied in Phase 1, depending on the number of dose levels evaluated. To date, 52 patients have been enrolled with 43 dosed in sites in North America.

Phase 2a: For the initial opening of this portion of the study, patients will be enrolled into 3 cohorts only: Cohorts 1 (FL), 3 (aggressive NHL [aNHL]), and 4 (CLL/SLL). Further cohorts may be opened or closed and the starting dose for patients may be adjusted at the discretion of the Sponsor, and the Sponsor will notify the Investigators/site when the other cohorts will be open or closed to enrollment or when the starting dose is adjusted. Initial enrollment into any cohort will be up to 20 patients; cohorts may be expanded to 40-50 evaluable patients. A total of approximately 240 patients is planned in the Phase 2a portion of the study. If fewer than 2 responses are seen in the first 20 patients, enrollment in the cohort will be closed, as the upper bound (UB) of the 95% confidence interval would be approximately 25%. If 2 or more responses are seen, the cohort may be expanded. With 40 patients in a cohort, an observed response rate of 30% will have a 2-sided exact 95% confidence interval (CI) of (16.6%, 46.5%); an observed response rate of 20% will have a 2-sided exact 95% CI of 9.1%, 35.7%.

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations used in this study protocol are shown in the table below. Specialist terms, including response criteria, are defined in Table 3.

Abbreviation	Expansion
ABC	Activated B-cell like diffuse large B-cell lymphoma
Ae	Amount of drug excreted in urine over the sampling interval
AE	Adverse event
ALKP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aNHL	Aggressive non-Hodgkin lymphoma
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell therapy
AST	Aspartate aminotransferase
Au	Amount of drug excreted into urine
AUC	Area under the curve
BCR	B-cell Receptor
BID	Twice a day
BR	Bendamustine and rituximab
BRAT	bananas, rice, applesauce, toast
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen (chemotherapy regimen)
CBC	Complete blood count
CFR	Code of Federal Regulations
CHOP	Cyclophosphamide, doxorubicin hydrochloride, vincristine (formerly oncovin) and prednisolone (chemotherapy regimen)
CIRS	Cumulative Illness Rating Scale
CL	Clearance
CLL	Chronic lymphocytic leukemia
CLr	Renal clearance
$C_{max/min}$	Maximum/minimum observed concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CR	Complete response
CRP	C-reactive protein
CRF	Case report forms

Abbreviation	Expansion
CRO	Contract research organization
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
DSMB	Data Safety Monitoring Board
dL	Deciliter
DLBCL	Diffuse Large B-cell Lymphoma
DLCO	Diffusion capacity of carbon monoxide
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
ESR	Erythrocyte sedimentation rate
FcR	Fc Receptor
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FFPE	Formalin-fixed paraffin embedded tissue
FISH	Florescence in situ hybridization
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FVC	Forced vital capacity
GCB DLBCL	Germinal center B-cell like Diffuse Large B-cell Lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GLP	Good Laboratory Practices
HCO_3	Bicarbonate
HCT-CI	Hematopoietic Cell Transplantation Co-Morbidity Index
HDPE	High Density Polyethylene
hERG	human ether-à-go-go-related gene
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
hr	Hour

Abbreviation	Expansion
HSCT	Hematopoietic stem cell transplant
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
IC_{90}	90% maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	Identification
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IND	Investigational New Drug
iNHL	Indolent non-Hodgkin lymphoma
INR	International Normalized Ratio
IRB	Institutional Review Board
IR	Immediate Release
ITP	Immune Thrombocytopenic Purpura
IV	Intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWG	International Working Group
JAK	Janus kinase
kg	Kilogram
LCMS	Liquid Chromatography Mass Spectrometry
LDH	Lactic dehydrogenase
LPL	Lymphocytoplasmacytic lymphoma
LLN	Lower Limit of Normal
LVEF	Left ventricular ejection fraction
MAD	Maximum Administered Dose
MALT lymphoma	Mucosa Associated Lymphoid Tumor
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
mSWAT	Modified Severity Weighted Assessment Tool
mg	Milligram
min	Minute
MITT	Modified Intent to Treat
mL	Milliliter

Abbreviation	Expansion
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
ORR	Overall response rate (CR + PR)
PCP	*Pneumocystis carinii* (aka *Pneumocystis jirovecii*) Pneumonia
PTCL	Peripheral T-cell lymphoma
PCR	Polymerase Chain Reaction
PD	Progressive disease or Pharmacodynamic
PET	Positron-Emission Tomography
PK	Pharmacokinetic
PI	Principal Investigator
PMA	Phorbol 12-myristate 13-acetate
PO	Orally
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
q12h	Every 12 hours
q24h	Every 24 hours
Q	Every
QD	Once daily
R-CHOP	Rituximab + CHOP (defined earlier)
RBC	Red Blood Cells
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIEP	Serum immunoelectrophoresis
SPEP	Serum protein electrophoresis
SLL	Small lymphocytic lymphoma

Abbreviation	Expansion
SOC	Standard of care or (MedDRA) system organ class
SS	Sézary Syndrome
ss	Steady state
SPD	Sum of the perpendicular diameters
STD_{10}	Severely toxic dose in 10% of rodents
SUSAR	Suspected unexpected serious adverse reaction
SYK	Spleen Tyrosine Kinase
$t_{½}$	Half-life
$T_{max/min}$	Time to maximum/minimum observed concentration
TEAE	Treatment emergent adverse event
µL	Microliter
µM	Micromolar
ULN	Upper limit of normal
USP	United States Pharmacopeia
VS	Vital signs
Vss	Volume at steady state
WBC	White blood cell(s)
WM	Waldenström's macroglobulinemia

Table 3: Protocol-specific List of Specialist Terms and Terms Used for Response Criteria

Specialist Term	Expansion and Definition
aNHL	Aggressive Non-Hodgkin lymphoma, defined as DLBCL, FL3B, MCL, and transformed NHL (definitions provided below).
Clinical Benefit	CR + PR + SD, PFS, and DOR.
CR	Complete response. Criteria vary by disease type.
DLBCL	Diffuse large B-cell lymphoma.
DOR	Duration of response: Time from the first documentation of PR or CR to the earlier of the first documentation of disease progression or death from any cause.
Intolerant	Discontinuation due to previous therapy due to a clinically significant adverse event.
FL/iNHL	Follicular lymphoma/indolent Non-Hodgkin lymphoma.
FL Grade 3B	Follicular lymphoma, Grade 3 B.
LNR	Lymph node response: The proportion of patients who achieve a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes.
MAD	Maximum administered dose: The MAD is defined as the highest dose level achieved in this study suitable for further investigation and will be declared the RP2D. If the MTD is not achieved, the highest studied dose will be declared the MAD and become the RP2D.
MCL	Mantle cell lymphoma.
MRD-	Minimum residual disease negativity: < 1 CLL cell in 10,000 leucocytes.
MRD+	Minimum residual disease positivity: ≥ 1 CLL cell in 10,000 leucocytes.
MTD	Maximum tolerated dose: Per the National Cancer Institute (NCI) Dictionary of Cancer terms, the MTD is "the highest dose of a drug or treatment that does not cause unacceptable side effects [6]."
ORR	Overall response rate: Defined as CR+PR.
PFS	Progression-free survival time: Time from the start of cerdulatinib treatment to the earlier of the first documentation of disease progression or death from any cause.
PR	Partial response: Criteria vary by disease type.
Relapsed Disease	Progression or recurrence of disease after documentation of response (CR or PR) ≥ 6 months since last treatment.
Refractory Disease	Progression on treatment, SD, or PR, or better, with progression < 6 months after any prior treatment.
RP2D	Recommended Phase 2 dose: The RP2D is the beginning dose recommended for Phase 2 clinical trials. For the purposes of this protocol, the MTD will be declared the RP2D. If the MTD is not declared, the MAD will be declared the RP2D.
SD	Stable disease: Criteria vary by disease type.
TTR	Time to treatment response: Time from the start of cerdulatinib treatment to the first documentation of CR or PR.

1.0 INTRODUCTION

1.1. Cerdulatinib (PRT062070)

Cerdulatinib (PRT062070) is an orally available, reversible, small molecule ATP competitive inhibitor of Spleen Tyrosine Kinase (SYK) and the Janus kinase (JAK) family that will be developed for the treatment of patients with B-cell malignancies, including non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia/small lymphocytic lymphoma CLL/SLL.

SYK, as a key component of Fc receptor signaling and of the BCR signaling pathway, has been demonstrated to be an important target in the disruption of cell survival signals mediated through BCR. It has been suggested that SYK may mediate survival signals in DLBCL, Mantle Cell Lymphoma (MCL), and FL [7-9]. The JAK/STAT pathway, important in cytokine signaling has also been reported to be activated in B cell lymphomas and the resistance of some DLBCL appears related to mutations that drive NFkB-mediated JAK/pSTAT3 activation [10]. CLL is another B-cell malignancy that appears to be dependent on BCR and thus SYK signaling [11]. Additionally, several cytokines have been reported to be increased in CLL and may be important in promoting CLL cell survival and proliferation through interaction with the tumor microenvironment [12]. The cytokines, IL-2, IL 4, and INF-α have been shown to promote CLL cell survival through the anti-apoptotic effects of up-regulation of BCL2 family proteins [13-15]. Studies have also shown that disruption of cytokine signaling via inhibition of JAK has the potential to reverse the cytoprotection provided to CLL cells by the tumor microenvironment [16].

Please refer to the Investigator's Brochure (IB) for more details.

1.2. Pharmacology Studies of Cerdulatinib

Multiple *in vitro* and *in vivo* pharmacology studies have been undertaken to evaluate the activity of cerdulatinib. Cerdulatinib was studied *in vitro* against a panel of purified kinase assays followed by specific cellular potency assays against SYK, JAK1, JAK2, JAK3, and TYK2. Significant potency was observed against signaling pathways utilizing SYK, JAK1, JAK3, and TYK2. SYK-dependent BCR signaling and functional responses were inhibited with a half maximal inhibitory concentration (IC_{50}) in the range of 0.1 to 0.5 µM. In cytokine signaling and functional response assays, inhibition against pathways utilizing JAK1/3 (Interleukin (IL)-2, IL 4) and JAK1/JAK2/TYK2 (IL-6) was observed, with IC_{50} values ranging from 0.15 to 0.9 µM. Cerdulatinib induces growth arrest and apoptosis in B-cell tumor cell lines and the viability of primary CLL cell cultures was also adversely affected in a dose dependent manner.

The *in vivo* effects of cerdulatinib have been studied in B-cell tumor xenografts, in a rodent model of idiopathic thrombocytopenic purpura (ITP), and in rodent models of arthritis. In the subcutaneous xenograft study, Ramos (Burkitt's lymphoma line) tumor growth was measured at various intervals. Inhibition of tumor growth was found to be comparable to that of vehicle controls. The lack of efficacy was likely the result of inadequate exposure of cerdulatinib, where

Cave plasma and tumor concentrations at the highest dose were below the level known to demonstrate inhibition of Ramos cell viability *in vitro*.

In an effort to overcome the challenges of the poor pharmacokinetics (PK) in mice, an intravenous (IV) tumor model was utilized, in which mice received an IV injection of Ramos cells, followed by cerdulatinib after 3 days of tumor growth. Time to hind limb paralysis, a marker of tumor growth and the primary efficacy endpoint, was significantly delayed in animals treated with cerdulatinib at a dose of 30 mg/kg twice daily (BID).

Cerdulatinib was also studied in a model of chronic BCR stimulation and splenomegaly. BCR stimulation and subsequent splenomegaly were induced in mice following injections of an anti-mouse BCR antibody. Doses of 15 mg/kg or greater were effective in reducing the splenomegaly compared to that observed in vehicle-treated animals. In a murine model of ITP, Fc receptor (FcR) mediated antibody-induced platelet clearance was significantly inhibited by treatment with cerdulatinib at a dose of 30 mg/kg, affirming the ability of this compound to interfere with SYK -dependent FcR signaling.

Two rodent models of arthritis have demonstrated the ability of cerdulatinib to interfere with SYK and JAK-mediated inflammation. In the mouse passive anti-collagen antibody induced arthritis (CAIA) model, inflammation and swelling were completely inhibited following cerdulatinib treatment at 30 mg/kg BID. In the rat collagen-induced arthritis model (CIA), treatment with cerdulatinib was initiated following the observation of paw inflammation. Progression of the arthritis and inflammation were completely suppressed in animals treated with cerdulatinib at doses of 5 mg/kg BID or higher.

The PK properties of cerdulatinib were evaluated in mouse, rat, dog, and monkey following IV and oral (po) dosing. Systemic clearance (CL_{ss}) was much higher in the mouse compared with CLss in rat, dog, and monkey. The volume of distribution (V_{ss}) was also highest in the mouse compared to other species. The apparent terminal half-life ($t_{½}$) ranged from 1.16 to 15.9 hours after IV administration. Cerdulatinib was well absorbed in rat and monkey (oral bioavailability; F = 22.3-30.9%) and completely absorbed in dog (F = 113%).

In the rat, the PK of cerdulatinib was non-linear following both IV and po administration. Between 1 and 10 mg/kg IV, the clearance of cerdulatinib decreased from 14.4 mL/min/kg to 7.81 mL/min/kg. Following po dosing at 1, 10, or 50 mg/kg, $AUC_{0-\infty}$ increased greater than dose-proportionally from 1 to 50 mg/kg. These data suggest that certain elimination pathways may be saturated at higher doses, resulting in a greater than dose-proportional increase in exposure.

In the dog, non-linear PK was observed following po dosing at 25 mg/kg. After 5 days of dosing, the exposure of cerdulatinib on Day 5 was higher than expected when comparing AUC_{0-24} on Day 5 to $AUC_{0-\infty}$ on Day 1. However, when compared to the exposure following administration of single po doses of 5, 15, or 50 mg/kg, the dose-normalized $AUC_{0-\infty}$ of the 15 and 50 mg/kg were lower than that of the 5 mg/kg. Therefore, the PK of cerdulatinib in the dog is possibly influenced by both some type of saturation of clearance process(es) and the limited absorption of the compound.

Protein binding for cerdulatinib in mouse, rat, dog, cynomolgus monkey, and human plasma was 91.7, 95.6, 83.2, 88.1, and 89.5%, respectively. Studies of bile-duct cannulated rats have shown that the major route of elimination for cerdulatinib appears to be metabolism. Cerdulatinib can be metabolized by CYPs 1A1, 1B1, 2J2, and 3A4. Oxidative metabolism appears to be the major route of metabolism of cerdulatinib by rat, dog, monkey, and human liver microsomes and hepatocytes.

The capacity of cerdulatinib to inhibit the major human liver CYP isozymes (CYPs 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4) was evaluated using pooled human liver microsomes and isozyme specific probe substrates. Cerdulatinib did not demonstrate significant inhibition at concentrations up to 50 μM. With respect to time-dependent inhibition, cerdulatinib demonstrated significant inhibition (≥ 30%) of CYP3A4 at 50 μM but not at 10 μM. Subsequently, it was found that cerdulatinib 0.3 to 1 μM decreased CYP3A4 mRNA and activity levels. Therefore, it is possible that cerdulatinib could affect the levels of co-administered drugs that are metabolized by CYP3A4 similar to a CYP inhibitor.

1.3. Safety Pharmacology Studies

The cardiovascular safety of cerdulatinib was assessed in both *in vitro* and *in vivo* studies. In a non-Good Laboratory Practices (GLP) human ether-à-go-go-related gene (hERG) radio-ligand binding displacement assay, cerdulatinib (10 and 50 μM) generated 10% and 34% inhibition of binding to the hERG receptor. In a non-GLP *in vitro* patch clamp study using transfected HEK 293 cells, cerdulatinib (50 μM) inhibited the potassium channel by 42%, compared to 69% for the positive control. In the subsequent GLP patch clamp study, 30 μM cerdulatinib resulted in a 38% inhibition of IKr tail current density. A non-GLP *in vitro* study of the effect of cerdulatinib on action potential duration was conducted in isolated Purkinje fibers from canine hearts. Cerdulatinib did not prolong action potential durations up to 50 μM concentration. Additionally, no changes were observed in action potential amplitude or resting membrane potential of the Purkinje fibers. These data suggest there is low potential for cerdulatinib to interact with the hERG or other cardiac ion channels.

In vivo studies included a non-GLP study of the effect of cerdulatinib on hemodynamic parameters in anesthetized rats. The IV infusion of cerdulatinib had no effect on heart rate and blood pressure up to plasma concentrations of 5 to 10 μM. In a non-GLP study telemetrized dogs received 25 mg/kg cerdulatinib or vehicle. Telemetry data for QT interval, heart rate, systolic, diastolic and mean arterial blood pressure were recorded from 17 hours pre- to 48 hours post study drug. Mean plasma levels at C_{max} were 4.7 μM and were maintained > 2 μM for up to 6 hours. No changes in QTc interval were observed, heart rate increased by ~20 beats per minute for 7 hours but remained within the normal range, diastolic and mean arterial blood pressure were unchanged, and systolic blood pressure showed sporadic decreases (3 and 20 hours) that were not considered biologically meaningful. A GLP cardiovascular safety study was also performed in dogs. Dogs maintained normal sinus rhythm and no consistent changes in QT morphology were observed. A number of changes in R-R interval and in diastolic, systolic, and mean arterial pressure were noted, however, although statistically significant these changes were generally considered incidental and not adverse. The no adverse effect level (NOAEL) for this study was determined to be 50 mg/kg.

A GLP respiratory safety study was also conducted. Male rats received cerdulatinib at 0, 25, 30, or 60 mg/kg. There were no statistically significant changes in respiratory rate for any group. Non dose-dependent but statistically significant changes in tidal volume between 1 to 6 hours post dose, and changes in minute volume 24 hours post dose were considered spurious, and the no observed adverse effect level (NOAEL) for this study was determined to be 60 mg/kg.

A GLP central nervous system (CNS) safety pharmacology study was conducted in rats. Low arousal/reactivity to environment was observed at dose levels of 30 and 60 mg/kg. Statistically significant changes in motor activity were noted for males given 60 mg/kg. Similar but not statistically significant changes were observed in female rats. The NOAEL for cerdulatinib was considered to be 30 mg/kg in males and 60 mg/kg in females.

A non-GLP Side Effect Panel screen was performed to assess the ability of cerdulatinib to interact with neurotransmitter related receptors, steroid receptors, ion channels, prostaglandins, growth factors/hormones, brain/gut peptides, and enzymes. Of the 63 tested, cerdulatinib at a concentration of 10 μM significantly inhibited ligand binding to only 2 (adenosine [non-selective] neurotransmitter receptor [58%] and sodium [site 2] ion channel [47%]).

1.4. Nonclinical Toxicology Studies

Single dose toxicity studies of cerdulatinib, given by oral gavage, were conducted in mouse, rat, and dogs. Deaths occurred in mice receiving 1,000 mg/kg or more, and in rats receiving 300 mg/kg. Additional observations included scruffy coat, piloerection, and abnormal gait in mice receiving 300 mg/kg, and weight loss in rats receiving 100 mg/kg. Dogs developed vomiting, loose stools, and a transient decrease in neutrophils at a dose of 50 mg/kg; all symptoms/signs recovered within 24 hours.

Non-GLP repeat dose, dose-ranging studies were conducted in mouse, rat, and dog. In mice given 30, 100, or 300 mg/kg daily for 12 days, the NOAEL was 30 mg/kg/day. Body weight loss, bone marrow hypoplasia, enteropathy, lack of splenic germinal centers, and thymic depletion were noted at doses of 100 mg/kg or greater. In a similar study, rats received 4, 10, 30, or 100 mg/kg/day given in divided doses BID for 11 days. The NOAEL was determined to be 30 mg/kg. Deaths occurred at 100 mg/kg/day. Additionally, AST/ALT increased by 2 to 3×, and animals given 100 mg/kg/day were observed to have myocardial necrosis, hepatic necrosis, thymic lymphoid depletion, and severe bone marrow hypoplasia. Bone marrow hypoplasia was also observed in 25% of animals given 30 mg/kg/day, along with mild thymic lymphoid depletion and a decrease in body weight gain. Two non-GLP studies were conducted in dogs. Dogs were given 25 mg/kg/day for 5 days or 10, 15, or 20 mg/kg/day for 11 days. In the 5-day study reversible decreases in neutrophils and total WBC were observed without clinical chemistry changes. In the 11-day study, dogs given 20 mg/kg/day had decreased WBC, without effects on other hematological parameters.

GLP-compliant toxicology studies were conducted in the rat and dog. Sprague-Dawley rats were given 0, 2.5, 6.0, or 15 mg/kg/day of cerdulatinib by oral gavage for 28 days. Recovery animals were included in the 0 and 15 mg/kg/day groups; recovery group animals given 15 mg/kg/day died or were euthanized during the recovery period (Study Days 29 and 38), but the deaths were attributed to phlebotomy procedure. The primary finding in male rats receiving 15 mg/kg/day was a statistically significant decrease in body weight gain. All dose groups had fewer mean WBC, lymphocyte, neutrophil, monocyte, eosinophil, basophil, and reticulocyte numbers compared to vehicle treated animals, however the changes were within the reference range and thus not considered biologically meaningful. Both male and female rats had statistically significant increases in alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALKP), however the magnitude of the change was < 2x and findings did not correlate with gross or microscopic findings. All cerdulatinib-treated rats had spleen and thymus weights less than vehicle-treated rats. Changes related to the pharmacologic activity of cerdulatinib, or that were not dose-dependent or associated with gross or microscopic pathologic findings were considered not adverse. T-cell immune response was also assessed in this study. All main study animals were immunized with 0.5 mg Keyhole Limpet Hemocyanin (KLH) on Day 12. Analysis for Immunoglobulin G (IgG) and Immunoglobulin M (IgM) showed both an IgM and IgG response that did not appear to be affected by administration of cerdulatinib. The NOAEL was considered to be 6.0 mg/kg in male rats and > 15 mg/kg in female rats. Mean C_{max}/AUC for male rats at 6.0 mg/kg/day was 445 ng/mL/4,886 ng*hr/mL, while the mean C_{max}/AUC for female rats at 15 mg/kg/day was 2,737 ng/mL/31,391 ng*hr/mL.

A 28-day repeat dose study was also conducted in dogs. Dogs received 0, 0.75, 2.5, 5.0, or 50/20/15 (multiple dose reductions) mg/kg/day of cerdulatinib by oral gavage. One death occurred on Day 7 in the 50 mg/kg/day group; the remaining animals in this group were dose reduced to 20 mg/kg/day on Day 10, then again to 15 mg/kg/day on Day 13 and Days 16 to 22.

This group was terminated on Day 22. Vomiting and fecal changes were present in dogs treated at 2.5 mg/kg/day or more. Decreased activity was observed in animals receiving 5.0 mg/kg/day or more. T-lymphocyte counts were decreased in a dose-dependent fashion in all animals receiving cerdulatinib at doses of 0.75 mg/kg/day or more. B-lymphocyte counts were also generally lower. Reductions in indicators of erythroid mass and in reticulocyte counts were observed in the high dose group and in animals from the 2.5 and 5.0 mg/kg dose groups. Reductions in WBC, including neutrophil and lymphocyte counts were also seen in these 3 dose groups. All hematologic changes showed complete recovery by the end of the recovery period. Thymus and spleen weights were decreased in the 2.5 and 5.0 mg/kg dose groups. Microscopic findings considered related to cerdulatinib included hypertrophy of the zona fasciculata of the adrenal glands; changes, including atrophy of the submucosal glands, of the esophagus; multifocal necrosis of the epithelium of the kidney proximal convoluted tubules and basophilia of the proximal tubules (5.0 and 50/20/15 mg/kg); lymphoid depletion of the cervical lymph nodes, thymus, and spleen; multifocal degeneration of the epithelium of the seminiferous tubules of the testes, and multinucleated spermatids of the seminiferous tubules (2.5, 5.0, and 50/20/15 mg/kg). Changes in the bone marrow, including hypocellularity, increased myeloid to erythroid ratio, and reduced total erythroid counts were observed in animals from the 5.0 and 50/20/15 mg/kg dose groups. The NOAEL for cerdulatinib was determined to be 2.5 mg/kg/day for females and 0.75 mg/kg/day for males. The NOAEL was determined to be 0.75 mg/kg/day. At 0.75 mg/kg mean C_{max} ranged from 216 to 231 ng/mL while AUC ranged from 1,219 to 1,751 ng*hr/mL. At 2.5 mg/kg, the mean C_{max} in females was 733 ng/mL and AUC was 4,430 ng*hr/mL.

The genotoxic/mutagenic potential of cerdulatinib was studied in both a GLP-compliant AMES assay and in a GLP-compliant rat bone marrow micronucleus assay with Liver Comet Assay. Cerdulatinib showed a low potential for mutagenicity in the AMES assay. Similarly, results of the rat bone marrow micronucleus assay showed a low probability that cerdulatinib is genotoxic or mutagenic (no DNA breaks or increased nuclear fragments).

For the Phase 1 trial, a starting dose of 15 mg QD has been proposed based on the STD_{10} in rats of 15 mg/kg. This dose is predicted to provide a steady state C_{max} and AUC of approximately 28 ng/mL (0.06 μM) and 225 ng*hr/mL, respectively, which is expected to yield C_{max} and AUC exposures of 8-fold and 7-fold lower than the no observed adverse effect level (NOAEL) in the dog of 0.75 mg/kg/day.

Thus, the pharmacology and nonclinical safety data described above support this initial proposed clinical trial of cerdulatinib, which is designed to identify the maximum tolerated dose (MTD), evaluate the safety profile, and assess the pharmacokinetic (PK) profile of cerdulatinib in patients with relapsed/refractory lymphoid malignancies.

1.5. Cerdulatinib Phase 1 Interim Results

The Phase 1 portion of the study is closed to enrollment.

Cerdulatinib data were presented at the 2015 American Society of Clinical Oncology meeting in June 2015 [17]. Doses studied included 15 to 65 mg po daily. Data for 30 patients demonstrated multiple nodal responses, and 4 patients demonstrated partial responses (PRs): at 30 mg in 1 patient with del 17p CLL who had relapsed after 6 prior therapies; at 45 mg in 1 patient with CLL who had received 4 prior therapies and 1 patient with follicular lymphoma (FL) who had received 3 prior therapies; and at 65 mg in 1 patient with a transformed diffuse large B-cell lymphoma (DLBCL; MYC, BCL2, and BCL6 expression by immunohistochemistry [IHC]) who had relapsed approximately 1 year after 1 prior therapy. No dose-limiting toxicities (DLTs) were observed as of that time. The PK parameters, specifically the half-life ($t_{½}$ of ~24 hours) and a 2:1 peak-trough ratio, indicated the suitability of once-daily dosing with cerdulatinib. Evidence of pharmacodynamic (PD) activity was observed for multiple markers of inflammation and cytokines, as well as complete inhibition of peripheral blood SYK and JAK signaling pathways.

After evaluation of the 65 mg dose cohort was completed, dose escalation proceeded to the 100 mg dose level. Pharmacokinetic (PK) findings from the 100 mg daily dose level were consistent with those from the 40 to 65 mg dose levels, indicating a plateau in exposure. Further analysis indicated the likely cause of this was cerdulatinib solubility.

A 45 mg twice daily (BID) dosing cohort was studied, which showed an increase in AUC and minimum and maximal concentrations (C_{min} and C_{max}, respectively). The 45 mg BID level roughly doubled the exposure relative to the 40 to 100 mg once daily (QD) average, achieving steady-state C_{min} and C_{max} of 1.5 and 1.8 μM, respectively. Under this dose regimen, 1 patient with FL achieved a PR, with what appeared to be a rapid (within 1 week) onset of palpable tumor reduction. Another patient with CLL experienced rapid lymphocytosis, whereas a refractory FL patient demonstrated stable disease (SD). The 45 mg BID dose regimen, however, resulted in 2 DLTs: 1 patient experienced pancreatitis within 2 weeks of dosing, and a second patient experienced Grade 3 fatigue. These findings were discussed at regularly scheduled conferences with the Investigator, during which it was determined that this dose regimen was not tolerated. Of note, the 2 patients with DLTs at 45 mg BID did not achieve the highest exposures at this dose level. Thus, we aggregated all data from the escalation portion of the study to date to explore the PK profile.

All AEs of Grade 3 or higher and all SAEs (including 2 fatal SAEs) considered to be related to cerdulatinib reported during the Phase 1 portion of the study in 43 dosed patients are summarized in Table 4 and Table 5, respectively. (Data cutoff is of 25 March 2016; although Phase 1 is closed to enrollment, dosing with cerdulatinib is still ongoing in several patients enrolled under Phase 1 who have been rolled over into the Phase 2a portion of the study.)

Table 4: Grade ≥ 3 Adverse Events Related to Cerdulatinib by MedDRA Preferred Term: Phase 1 Portion (Completed) of Study 13-601 (N=43)

AEs by MedDRA Preferred Term	Total Number of Patients (N=43)	
	Number (%) of Patients with Grade ≥ 3 AE (N=43)	Number (%) of Patients with AE Any Grade (N=43)
Diarrhea	4 (9.3)	27 (46.5)
Nausea	1 (2.3)	11 (25.6)
Abdominal pain	2 (4.7)	8 (18.6)
Pancreatitis	1 (2.3)	1 (2.3)
Fatigue	5 (11.6)	15 (34.9)
Anemia	3 (7)	5 (11.6)
Neutropenia	3 (7)	5 (11.6)
Thrombocytopenia	1 (2.3)	3 (7)
Febrile Neutropenia	1 (2.3)	1 (2.3)
Pancytopenia	1 (2.3)	1 (2.3)
Neutrophil count decreased	2 (4.7)	3 (7)
LDH increased	1 (2.3)	2 (4.7)
AST increased	1 (2.3)	1 (2.3)
Decreased appetite	1 (2.3)	7 (16.3)
Hyponatremia	1 (2.3)	2 (4.7)
Pneumonia	2 (4.7)	2 (4.7)
Lung infection	1 (2.3)	1 (2.3)
Pneumocytsis jirovecii pneumonia [a]	1 (2.3)	1 (2.3)
Macular rash	1 (2.3)	1 (2.3)
Hypotension	1 (2.3)	2 (4.7)

AE = Adverse event; MedDRA = Medical dictionary for regulatory activities

Note: Data cutoff: 25 March 2016.

[a] Fatal.

Source: Data on file at Portola (clinical study database). The Phase 1 portion of the study is closed to enrollment; however, some patients enrolled under Phase 1 are still receiving cerdulatinib in Phase 2a.

Table 5: All Serious Adverse Events Related to Cerdulatinib by MedDRA Preferred Term: Phase 1 Portion (Completed) of Study 13-601 (N=43)

Serious Adverse Event by MedDRA Preferred Term	Number (%) of Patients (N=43)
Anemia	1 (2)
Blood and Lymphatic System Disorders - Other, specify: Pancytopenia	1 (2)
Diarrhea	1 (2)
Febrile Neutropenia	1 (2)
Fever	1 (2)
Hypotension	1 (2)
Lung infection [a]	1 (2)
Nausea	1 (2)
Pancreatitis	1 (2)
Pneumonia	1 (2)
Pneumocytsis jirovecii pneumonia [a]	1 (2)

AE = Adverse event; MedDRA = Medical dictionary for regulatory activities

Note: Data cutoff: 25 March 2016.

[a] Fatal.

Source: Data on file at Portola (clinical study database). The Phase 1 portion of the study is closed to enrollment; however, some patients enrolled under Phase 1 are still receiving cerdulatinib in Phase 2a.

Pharmacokinetic modeling and exploration of the PK/PD and PK/AE data from the Phase 1 portion indicated that a dose of 35 mg BID should provide adequate exposure as well as inhibition of the desired targets of cerdulatinib. Further explanation of the data and rationale for dosing during Phase 2a portion of the study is provided in Section 3.1.2.2.

During Phase 1, PRs have been observed in CLL (including 17p deleted CLL), FL, and transformed follicular lymphoma. CR was observed in 2 FL patients. Responses typically occurred after 2 cycles and have been durable in several patients [18].

1.6. Background on the NHL in the Study

The non-Hodgkin lymphomas (NHLs) are a diverse group of disorders of proliferating B, T, or NK cells, and collectively, NHL is the seventh leading site of new cancer cases in the United States (US) in men and women [19]. In the US, B-cell lymphomas are diagnosed in approximately 85 to 90% of people, and T-cell NHL comprises the majority of the remaining 10 to 15%. In 2015, approximately 72,000 people in the US will be diagnosed with NHL, and there will be nearly 20,000 deaths.

The overall incidence of NHL has increased since the 1970s through the 1990s, partially due to human immunodeficiency virus (HIV). However, the incidence of NHL in older individuals is also increasing, and thus the median age of patients with NHL has increased as well. Many of these older patients have multiple comorbid conditions that complicate NHL treatment [19, 20].

In the past 10 to 15 years, the treatment of NHL and CLL/SLL has changed from treatment regimens comprising a variety of combinations of cytotoxic therapeutics to the introduction of multiple novel therapeutic modalities. Perhaps the most significant of these have been the anti-CD20+ antibodies (most prominently rituximab); however, novel purine/pyrimidine analogues (fludarabine) and alkylating agents (bendamustine) have also resulted in significant changes to the treatment paradigms for both NHL and CLL/SLL. More recently, novel tyrosine kinase inhibitors targeting components of the B-cell receptor (BCR) signaling pathway (fostamatinib, idelalisib, ibrutinib) have entered clinical trials. Response rates have demonstrated the dependency of many of the NHL subtypes, and particularly CLL/SLL, on BCR signaling for survival [20-23].

1.6.1. Aggressive B-cell Lymphomas

Diffuse large B-cell lymphoma (DLBCL) accounts for 30 to 40% of B-cell NHL [19, 24]. Follicular lymphoma, Grade 3B (FL3B), accounts for < 10% of all FLs and behaves similarly to DLBCL [25]. Similarly, transformed NHL refers to a typically more indolent lymphoma that has transformed to a more aggressive lymphoma, with varying reported rates of transformation [26]. Mantle cell lymphoma (MCL) accounts for 6% of NHL and often can have a more aggressive course [19]. The underlying biology behind the various aggressive lymphomas is diverse and may involve mutations or overexpression of MYC, BCL2, and other oncogenes [19, 24, 26, 27]. SYK inhibition, as well as inhibition of various cytokines in the JAK-STAT pathway, demonstrated activity against various B-cell lymphoma cell lines [1].

The typical treatment for the more aggressive lymphoma consists of an anti-CD20 antibody, rituximab, combined with cytotoxic chemotherapy such as cyclophosphamide, doxorubicin hydrochloride, vincristine (formerly oncovin), and prednisolone (CHOP; i.e., the R-CHOP regimen). This can produce durable remissions in a number of patients and lead to cure. Patients who relapse are often treated with a variety of salvage regimens and may receive high-dose chemotherapy with stem cell rescue, which in some cases may also be curative [19, 24-26]. Unfortunately, not all patients are candidates for high-dose chemotherapy with stem cell rescue due to a variety of factors such as age and organ dysfunction (cardiac, pulmonary, renal, hepatic); thus, these patients are in need of alternative therapies [28].

Unfortunately, limited treatment options exist for the patient who has a disease relapse or is refractory to therapy. In the case of MZL, ibrutinib, an inhibitor of BTK, has been approved for relapsed/refractory patients [29]. There are limited treatment options for patients with relapsed/refractory DLBCL, transformed NHL, MCL, cell lymphoma, or FL3B [19, 26, 30, 31]. Newer agents are needed.

1.6.2. Rituximab in the Treatment of B-cell NHL

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed on normal and malignant B-cells [32, 33]. Rituximab's mechanism of action involves antibody

dependent cellular cytotoxicity (ADCC), complement mediated cytotoxicity (CDC), and direct induction of apoptosis [33].

Rituximab was originally approved by the US FDA in 1997 for the treatment of relapsed or refractory low-grade NHL. Subsequently, it was approved in combination with chemotherapy for both front-line follicular NHL, diffuse large B-cell NHL, and as chemotherapy in previously treated or untreated CLL [32, 34, 35]. Rituximab is also approved as a maintenance therapy for low-grade NHL. It has also been used in the treatment of other B-cell NHL such as relapsed Waldenstrom's macroglobulinemia (WM) and MCL [19, 32, 36].

The drug is given in a variety of doses and schedules and is generally well tolerated. Several types of adverse events (AEs) have been observed with rituximab administration when used for the treatment of NHL, including infusion reactions, tumor lysis syndrome, hematotoxicity, and increased incidence of infections [33, 34].

In combination with chemotherapy, rituximab-containing regimens have consistently demonstrated improvements in overall survival (OS), and overall response rate (ORR) vs. chemotherapy alone. It is now a mainstay of B-cell NHL therapy [19, 37].

1.6.3. T-cell NHL (PTCL, CTCL)

T-cell NHL comprises approximately 10 to 15% of the total cases of NHL, resulting in approximately 7,000 to 10,000 cases/year in the US [19, 38]. The 2008 World Health Organization (WHO) classification has a multitude of subtypes of PTCL, and the majority of them are peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma. In general, patients with PTCL have an inferior survival rate as compared to patients with B-cell NHL [19, 38, 39]. SYK is expressed in PTCL samples, a SYK-ITK fusion gene has been identified in PTCL, and the JAK/STAT pathway has been implicated in this disease as well [40-42].

Typical front-line treatment of PTCL consists of CHOP or other intense chemotherapy, albeit with inferior outcomes as mentioned above. There are several agents approved for treatment in the relapsed/refractory setting, but all have response rates of 25 to 30% and response durations of approximately 1 year or less [19, 38, 39, 43-45]. Both autologous and allogeneic stem cell transplantation have also been used as salvage therapy for relapsed patients with PTCL with some evidence of efficacy, but little, if any randomized data exists [46, 47].

For patients who relapse after, or are refractory to multiple therapies, the prognosis is dismal and new therapies are needed.

The cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of skin-homing lymphomas. The majority of CTCLs comprise Mycosis Fungoides (MF) and Sézary Syndrome (SS) [19, 48]. In the early stages of CTCL, skin directed therapies such as phototherapy,

steroids, or nitrogen mustard are administered [19, 48, 49]. For patients whose disease has progressed after treatment with the skin-directed therapies mentioned above, systemic therapies are used. Several therapies are currently approved or used for CTCL and include bexarotene, vorinostat, and romidepsin [19, 43, 48, 50]. Systemic chemotherapy is also used as a treatment for patients with advanced disease and SS [19]. Patients with CTCL have a number of supportive care concerns and comorbid conditions, including pruritus and infectious complications. Pruritus can have a major impact on patients' quality of life and may be related to several cytokines [51-53]. Multiple genomic aberrations have been described in CTCL that involve the JAK/STAT pathways [54].

There is no standard agreed upon algorithm for the treatment of advanced CTCL, and for patients with advanced disease whose disease relapses after standard therapy, newer therapies are needed.

1.6.4. Follicular Lymphoma and Other Indolent Lymphomas (iNHL); (FL/iNHL)

Follicular lymphoma is the most common indolent NHL (iNHL), accounting for about 20 to 30% of all B-cell NHL [19, 55]. Nearly 90% of cases have a translocation [15, 19], resulting in deregulated expression of BCL2. Follicular lymphoma has several grades depending on various histologic features; however, Grade 3B is usually treated like DLBCL [19, 25, 55]. Although they have differing histologies, the other iNHLs such as SLL (discussed below), Waldenström's macroglobulinemia (WM), and marginal zone lymphoma (MZL) often have similar clinical presentations, histories, and treatments as does FL, and are often included in the iNHL category along with FL [56].

Although advanced disease is not curable, effective therapy is available for this disease. Therapy is usually initiated when symptoms are present or certain criteria are met [55]. Rituximab has had a major influence on the treatment of follicular lymphoma and other iNHLs. Typical front-line treatments include rituximab as a single agent, or combined with chemotherapy such as CHOP, bendamustine, or other agents [19, 55, 57]. These agents may also be used in the relapsed setting. High dose chemotherapy with autologous or allogenic stem cell rescue has also been used as a salvage therapy with some success as well [57, 58].

A certain percentage of FLs will transform into DLBCL, which is associated with a poor clinical outcome. The underlying reasons for transformation are unknown, and the risk of transformation is about 2 to 3% per year [26]. These patients are treated like patients with DLBCL.

For patients whose disease has progressed after multiple therapies, several agents have been used, and the PI3 kinase inhibitor, idelalisib, has been approved by the US FDA and other regulatory agencies for use in patients with FL whose disease has progressed after 2 prior therapies [19, 58, 59]. This agent has a response rate of over 50% and a median duration of response of 12.5 months [59]. Further agents are needed for patients with multiple relapsed and/or refractory FL and other iNHLs.

1.6.5. Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

CLL is the most prevalent leukemia in the western world. SLL is essentially a more nodal form of the disease without peripheral blood involvement [19, 55]. In 2015, there were an estimated 14,620 cases and 4,650 deaths from CLL/SLL.

CLL/SLL is grouped with the indolent lymphomas and is incurable; however, typically it is treatable. Depending on the stage, genetic/other prognostic factors and symptoms at diagnosis, patients may be observed initially and only treated when symptoms such as adenopathy or cytopenias develop [19, 55, 60].

There are a multitude of regimens available for therapy and the choice of 1 regimen or agent over another depends on the patient's prognostic factors, performance status, and symptoms. For more elderly patients with comorbidities, chlorambucil (alone or in combination with obinituzumab or ofatumumab, both anti-CD20 antibodies) can be used. The combinations have shown superior outcomes vs. single-agent chlorambucil [19, 60, 61]. Alternatively, bendamustine with rituximab can also be used. For more fit patients, fludarabine may be used in combination with rituximab and cyclophosphamide (for both upfront and relapsed/refractory patients) [19, 60, 61].

Unfortunately, patients will ultimately relapse or become refractory to most therapies. In some cases, patients may have a histologic transformation of their CLL to DLBCL (Richter's syndrome), and these patients have a poor prognosis [19, 62, 63]. For patients who relapse from previous cytotoxic therapies, such as bendamustine and rituximab, or fludarabine, cyclophosphamide and rituximab, the options are limited especially if the duration of response is fewer than 2 to 3 years [64]. Newer agents are available: Ibrutinib, an inhibitor of Bruton's tyrosine kinase (BTK) was recently approved for the treatment of CLL for patients with relapsed/refractory disease [21, 61, 65]. In addition, idelalisib, an inhibitor of PI3 kinase, was also approved for the treatment of CLL in combination with rituximab for patients with relapsed CLL with comorbidities [49, 66]. Lastly, venetoclax, an inhibitor of BCL2, has shown dramatic activity in relapsed/refractory CLL, although the patients treated in this study had CLL that was relapsed/refractory to fludarabine or alkylator-based therapy [67]. However, patients will relapse from or be refractory to these newer agents, and in the case of relapse from ibrutinib, the prognosis is dismal, with a median survival of approximately 3 months [68]. New therapies are needed for patients who progress or are refractory to the current ones.

In CLL, the detection of minimal residual disease (MRD) is an independent predictor of OS and PFS in patients treated with chemoimmunotherapy [69]. The prognostic value of achieving MRD negativity is unknown with newer pathway inhibitors, and it remains a patient of clinical investigation. MRD assessment has traditionally been done by flow cytometry (typical limit of detection at 1 in 10,000 cells), although other assessments that are perhaps more sensitive are being studied [69-71].

2.0 OBJECTIVES AND ENDPOINTS

See Table 3 for definitions of the specialist terms and response criteria used in the sections that follow.

2.1. Objectives

2.1.1. Phase 1 Objectives (Escalation)

2.1.1.1. Primary Objective

- To determine the maximum tolerated dose/maximum administered dose (MTD/MAD) of cerdulatinib in patients with relapsed/refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) or B-cell non-Hodgkin lymphoma (NHL).

2.1.1.2. Secondary Objectives

- To make a preliminary assessment of the antitumor activity of cerdulatinib in patients with relapsed/refractory CLL/SLL or B-cell NHL, as assessed by overall response rate (ORR), defined as complete response (CR)+ partial response (PR).
- To assess the safety and tolerability of cerdulatinib.
- To determine the pharmacokinetic (PK) profile of cerdulatinib.
- To evaluate the pharmacodynamics (PD) of cerdulatinib.

2.1.2. Phase 2a Objectives (Exploratory)

2.1.2.1. Primary Objective

- To assess the antitumor activity of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL, or CLL/SLL, as a single agent and in combination with rituximab for B-cell NHL.

2.1.2.2. Secondary Objectives

- To assess the duration of antitumor activity of cerdulatinib, amount of time to achieve tumor response, and magnitude of response.
- To further evaluate the PK profile of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL, alone or in combination with rituximab for B-cell NHL.
- To further evaluate the PD of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL, alone or in combination with rituximab for B-cell NHL.
- To assess tumor phenotype and genotype in relation to clinical response.
- To further evaluate the safety and tolerability of cerdulatinib in patients with specific subtypes of B-cell or T-cell NHL, or CLL/SLL.

- To evaluate the safety and tolerability of the combination of cerdulatinib with rituximab for B-cell NHL.

2.1.2.3. Exploratory Objectives

- To evaluate the relationship between markers of inflammation with clinical outcome and overall health as determined by the Global Health Assessment.
- To assess Minimal Residual Disease (MRD) status in CLL/SLL patients achieving a complete response/complete response incomplete blood count recovery/partial response (CR/CRi/PR) by flow cytometry. MRD negativity (MRD-) is defined as < 1 tumor cell in 10,000 leucocytes. MRD+ (MRD positivity) is defined as ≥ 1 tumor cell in 10,000 leucocytes.

2.2. Endpoints

2.2.1. Phase 1 Endpoints

2.2.1.1. Primary Endpoint

- The primary safety endpoint will be the incidence of DLT by dose level.

2.2.1.2. Secondary Endpoints

- ORR, defined as CR+PR.
- Clinical benefit rate, defined as CR + PR + SD, PFS, and DOR.
- Adverse event profile (classified by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE v4.0]) by dose level.
- Clinically significant changes in vital signs, physical exams by dose level.
- Changes in hematology and chemistry laboratory parameters by dose level.
- PK endpoints: PK profile at each dose level and overall, including C_{max}, AUC, and $t_{½}$.
- PD endpoints: Changes in biomarker data for a range of *ex vivo* assays.

2.2.2. Phase 2a Endpoints

2.2.2.1. Primary Endpoint

- The primary efficacy endpoint is ORR, defined as CR+PR.

2.2.2.2. Secondary Endpoints

- Duration of response (DOR), progression-free survival (PFS), time to treatment response (TTR), and lymph node response (LNR).
- Clinical benefit rate, defined as CR + PR + SD.
- Adverse event profile (classified by NCI-CTCAE v5.0) by dose level.
- Clinically significant changes in vital signs, physical exams by dose level.
- Changes in hematology and chemistry laboratory parameters by dose level.
- PD endpoints: Changes in biomarker data for a range of *ex vivo* assays.

2.2.3. Exploratory Endpoints

- Correlation in markers of inflammation with clinical response and overall health (Global Health Assessment).
- Assessment of percentage of CLL/SLL patients with status of MRD- in CLL/SLL patients achieving a CR/CRi/PR by flow cytometry.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design and Study Schema

This is an open-label, Phase 1/2a, multi-dose, multi-center trial of orally administered cerdulatinib with 2 phases:

- Phase 1: Dose-escalation portion, during which patients will receive single-agent cerdulatinib at their assigned dose level. The starting dose for this portion of the study will be 15 mg QD, administered in increasing doses until the MTD/MAD is identified.
- Phase 2a: Exploratory portion, consisting of 6 cohorts, defined by cancer type and prior therapy. Five cohorts will receive single-agent cerdulatinib, and 1 cohort will receive cerdulatinib plus rituximab administered IV during Cycle 1 on Days 1, 8, 15, and 22 and during Cycles 4, 6, 8, and 10 on Day 1 only. The starting dose of cerdulatinib during this portion of the study will be 30, 25, or 20 mg BID.

The Schedule of Assessments for Phase 2a is provided in Appendix 1.

3.1.1. Phase 1

3.1.1.1. Overall Description

Patients: The Phase 1 portion of the study will include patients with a histologically confirmed diagnosis of CLL/SLL or B-cell non-Hodgkin lymphoma.

Design: Eligible patients enrolled in sequential dose cohorts will receive once-daily, orally administered single-agent cerdulatinib at starting dose of 15 mg (15 mg po QD) in increasing dose levels until the MTD/MAD is identified. **An exception occurs on Days 2 and 3, during which patients on a QD schedule will not take study drug (see next paragraph**). If the MTD is not achieved, the highest studied dose will be declared the MAD and become the RP2D. (See Table 3 for definitions of cancer types.)

To allow for a single-dose PK assessment, patients on a QD dosing regime will take their first dose of cerdulatinib on Day 1 and their second and subsequent doses daily beginning on Day 4. **They will not take cerdulatinib on Days 2 or 3.** Starting with Day 4, patients will receive cerdulatinib once daily for a total of 28 days (one cycle) to assess the MTD/MAD. Patients on BID dosing schedules can dosing begin on Day 1 and continue cerdulatinib without interruption (i.e., these patients will not skip any days of the cycle). If cerdulatinib is well tolerated, patients may continue to receive cerdulatinib at their assigned dose in the absence of disease progression, unacceptable toxicity, or meeting of any other withdrawal criteria (Section 4.4).

One patient will be enrolled in each dose cohort until the first report of a Grade 2 or greater adverse event (AE). In the event of any Grade ≥ 2 AE in the single patient, an additional 2 patients, for a total of 3, will be enrolled in that dose cohort, and all subsequent dose cohorts will follow a "3 + 3" design. Dose escalation will be in 100% increments until a drug-related AE of Grade 2 or greater severity occurs. Thereafter, dose escalation will be in increments of up to 50% as determined following review by the Study committee. If a dose-limiting toxicity (DLT) occurs in 1 of the first 3 patients in a cohort, that cohort will be expanded to at least 6 patients. If ≤ 33% of six or more patients in a cohort experiences DLT, dose escalation may proceed. If in any cohort 2 or more of the first 3 patients or ≥ 33% of patients in a cohort develop DLT, dose escalation will cease, and that dose level will be declared intolerable. The prior dose level will be declared the MTD, and the cohort may be expanded to as many as 6 patients if fewer than 6 patients had been treated previously at that dose level in order to further characterize the PK and PD at that level. A total of 43 patients have been dosed. The study is closed to Phase 1 enrollment.

3.1.1.2. Rationale for Dose Selection in Phase 1 and Dose-Escalation Methods

The starting dose for the Phase 1 portion of the study was based on the severely toxic dose in 10% of rodents (STD_{10}) from a 28-day toxicology study in the rat, the most sensitive species, as defined by the S9 Guidance to Industry *"Nonclinical Evaluation for Anticancer Pharmaceuticals."* One-tenth of the STD_{10} of 15 mg/kg is recommended by the guidance to be the appropriate starting dose. After allometric scaling, and accounting for the average weight of human patients (70 kg), the total daily starting dose for cerdulatinib was determined to be 15 mg po once daily (QD). The dose-escalation methods accord with the principles described by Le Tourneau et al., for Phase 1 clinical trials [6].

3.1.2. Phase 2a

3.1.2.1. Overall Description, Including Rationale for Inclusion of T-cell Malignancies

Patients: The Phase 2a portion of the study will include patients with B-and T-cell malignancies (Table 6) who are believed to be able to tolerate therapy and who will provide interpretable results to further guide the development of cerdulatinib. In general, the malignancies being studied in this portion of the study were chosen based on the role of BCR signaling and/or the role of the JAK/STAT pathway in their disease as discussed in Section 1.0. The decision to include T-cell malignancies in the Phase 2a cohorts was based on SYK expression in PTCL, as well as the role of the JAK/STAT pathway in PTCL described in Section 1.6.3. A rituximab combination cohort (Cohort 2, see Table 6) was added to explore the activity of cerdulatinib with a known effective agent in the treatment of B-cell NHL.

Design: The Phase 2a portion will investigate 6 cohorts, each defined by cancer type and therapy (Table 6). Five cohorts will receive single-agent cerdulatinib administered orally, and 1 cohort with B-cell NHL (No. 2) will receive orally administered cerdulatinib *and* rituximab administered IV at 375 mg/m^2 during Cycle 1 on Days 1, 8, 15, and 22 and during Cycles 4, 6, 8, and 10 on Day 1 only.

Initial enrollment into *any* of the 6 cohorts will be up to 20 patients; each cohort may be expanded for a total of approximately 240 patients in the Phase 2a portion of the study.

Throughout the duration of the study, Portola will inform Investigators and sites regarding which cohorts are open and what starting dose of cerdulatinib (i.e., 30, 25, or 20 mg BID) should be administered to patients at the time of enrollment. Dose Modification Guidelines for Phase 2a are provided in Section 5.2.1.3.

Table 6: By-Cohort Inclusion Criteria for Phase 2a Cohorts

Cohort Number (short descriptor)	Inclusion Criteria
1 (FL)	Patients with FL Grade 1 to 3A who have received ≥ 1 prior treatment regimen.
2 (Combination Cohort)	Patients with FL Grade 1 to 3A who have received ≥ 1 prior treatment regimen. In addition to receiving cerdulatinib, this cohort will also receive rituximab IV at 375 mg/m^2 during Cycle 1 on Days 1, 8, 15, and 22 and during Cycles 4, 6, 8, and 10 on Day 1 only.
3 (aNHL)	Patients with aggressive NHL (aNHL), defined as DLBCL, FL 3B, MCL, and transformed NHL. These patients have relapsed from ≥ 1 but ≤ 3 prior cytotoxic chemotherapy regimens with an anti CD20 antibody, (e.g., R-CHOP, BR). Patients must have received an anthracycline based therapy unless anthracyclines were deemed inappropriate in the judgement of the investigator. Patients must have either relapsed following ASCT or not be candidates (ineligible) for ASCT, defined as meeting any of the following criteria [1]: a) age ≥ 70 years; b) DLCO < 50% by pulmonary function tests; c) FEV_1/FVC < 60% predicted by pulmonary function tests; d) LVEF < 45% by MUGA or echocardiogram; e) uncontrolled arrhythmia; f) calculated creatinine clearance (Cockcroft-Gault) ≤ 60 mL/min; g) other comorbidities (e.g., medical conditions or psychosocial conditions) that would likely result in an unacceptably high probability of treatment/transplant related morbidity and mortality in the judgement of the investigator (e.g., high HCT-CI, CIRS, scores); h) refusal of ASCT. (Note: Antibody drug conjugates (ADC) count as cytotoxic chemotherapy. Salvage chemotherapy prior to ASCT with or without maintenance therapy counts as one regimen.)
4 (CLL/SLL)	Patients with CLL/SLL who have received ≥ 1 prior treatment regimen.
5 (PTCL NHL)	Patients with PTCL NHL who have received ≥ 1 prior systemic treatment regimen for PTCL. In patients with CD30-expressing PTCL, prior treatment must include a CD30-directed antibody (e.g., brentuximab vedotin).
6 (CTCL NHL)	Patients with CTCL NHL who have received ≥ 1 prior systemic treatment regimen for CTCL.

ADC = Antibody drug conjugate; ASCT = Autologous stem cell therapy; aNHL = Aggressive non-Hodgkin lymphoma; BCR = B-cell receptor; BR = Bendamustine and rituximab; BTK = Bruton tyrosine kinase; CLL = Chronic lymphocytic leukemia; CIRS = Cumulative Illness Rating Scale; CTCL = Cutaneous T-cell lymphoma; DLBCL = Diffuse Large B-cell lymphoma; DLCO = Carbon monoxide diffusion capacity; FEV_1/FVC = Forced expiratory volume in 1 second/forced vital capacity; FL = Follicular lymphoma; FL 3B = Follicular lymphoma, Grade 3B; HCT-CI = Hematopoietic cell transplantation co-morbidity index; HSCT = Hematopoietic stem cell transplant; LEVF = Left ventricular ejection fraction; MUGA = Multiple gated acquisition; PR = Partial response; PTCL = Peripheral T-cell lymphoma; R-CHOP = Rituximab + cyclophosphamide, doxorubicin hydrochloride, vincristine (formerly oncovin), and prednisolone; SLL = Small lymphocytic lymphoma

Note: Patients who received any BCR pathway inhibitor (e.g., BTK inhibitors such as ibrutinib, or PI3 Kinase inhibitors such as idelalisib) and/or BCL2 pathway inhibitors (e.g., venetoclax), and were either intolerant to therapy or had relapsed/refractory disease following therapy are also eligible.

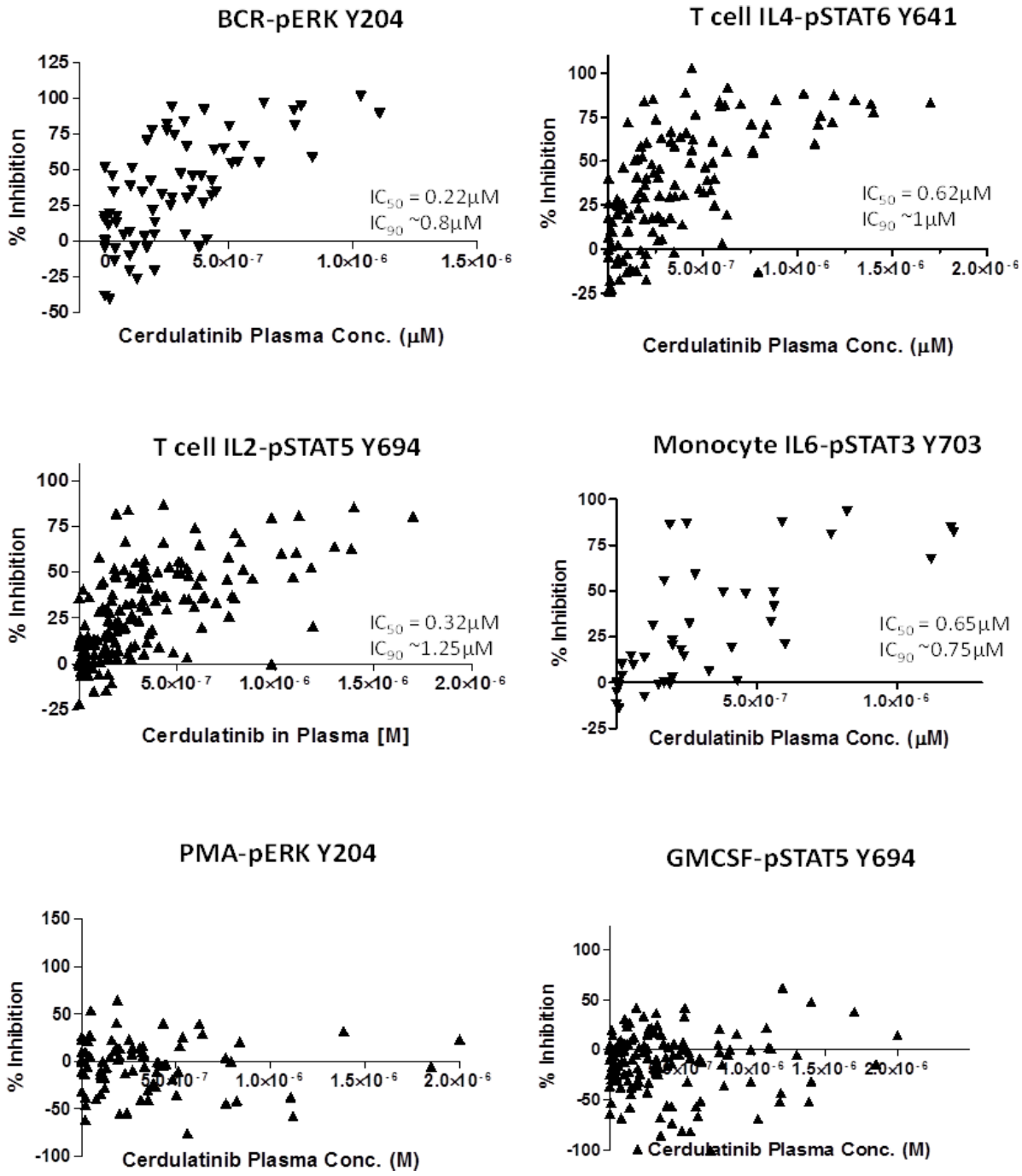
3.1.2.2. Rationale for Initial Starting Dose and Individual Dose Reductions

3.1.2.2.1. Rationale for Starting Dose

Under Amendment 4 the starting dose of cerdulatinib in the Phase 2a portion of the study was 35 mg BID based on the PK/PD and PK/AE relationships and PK modeling of the Phase 1 study (Section 1.5). Clinical PK/PD evaluations demonstrated that IC_{50}s in the 0.2 to 0.6 µM range suppress BCR and cytokine JAK/STAT signaling pathways (Figure 1). However, under Amendment 5, the starting dose was changed to 30 mg BID (rationale below), with subsequent dose reductions to 25 mg BID, 20 mg BID, and then 15 mg BID permitted (the rationale for individual dose titration strategy is in Section 3.1.2.2.2). Under Amendent 7 starting doses of 30, 25, or 20 mg BID may be explored to further investigate the relationships between cerdulatinib exposure, extent of SYK/JAK pathway inhibition, anti-inflammatory response, clinical response, and safety. The data overall will be used in the final determination of the appropriate dose for registration studies.

IC_{90} for BCR signaling is approximately 0.8 µM, and for JAK/STAT signaling ranges from 0.75 to 1.25 µM. The pathway inhibition is selective, as no inhibition of JAK2- or PKC-dependent signaling was observed. These data reflect pathway inhibition in peripheral blood, and therefore do not predict the level of inhibition in solid tumor.

Figure 1: Cerdulatinib Pathway Inhibition in Peripheral Blood



Conc = Concentration; IC_{50} = Half maximal inhibitory concentration; PK/PD = Pharmacokinetic/pharmacodynamic
Notes: PK/PD relationships are shown from peripheral whole blood assays. Percent inhibition relative to pre-dose signaling on Day 1 is plotted on the Y-axis, cerdulatinib plasma concentration in molar on the X-axis. Clinical PK/PD evaluations have demonstrated IC_{50}s in the 0.2 to 0.6 µM range to suppress BCR and cytokine JAK/STAT signaling pathways. IC_{90} for BCR signaling is approximately 0.8 µM, and for JAK/STAT signaling ranges from 0.75 to 1.25 µM.

Cerdulatinib was studied at multiple QD and BID dose levels and exhibited nonlinear PK at doses higher than 30 mg QD, with the exposure increasing approximately 3-fold as the dose was increased from 30 to 40 mg QD. Daily dose levels ranging from 40 to 65 mg demonstrated an exposure plateau above 30 mg QD, resulting in average steady-state C_{min} and C_{max} concentrations of 0.8 and 1.6 µM, respectively. The 100 mg QD dose resulted in lower overall exposure, possibly a consequence of drug precipitation in the gut. The 40 to 65 mg dose levels resulted in greater than 90% inhibition of the BCR signaling pathway, and greater than 75% inhibition of various JAK/STAT pathways (IL2, IL4, IL6) at steady-state C_{min}. Two PRs were observed at the 45 mg QD dose level, and a third at the 65 mg QD dose. The $t_{½}$ at these doses was approximately 24 hours. Hence, the drug properties are suitable for once daily dosing.

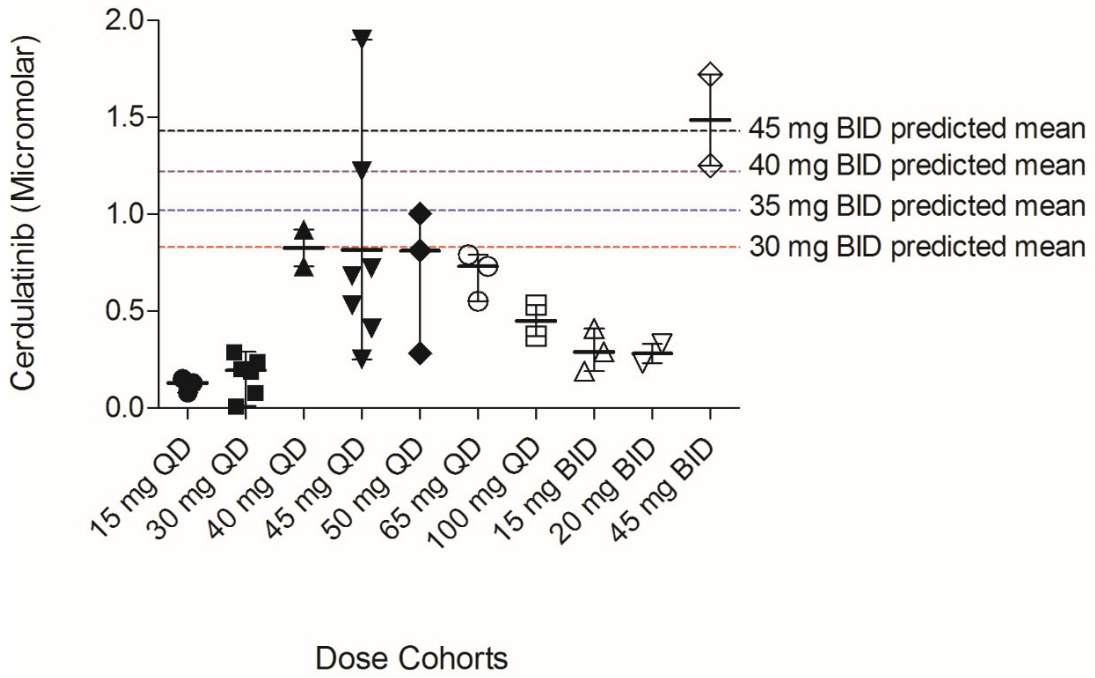
Based on pre-clinical tumor models, 1 µM cerdulatinib is sufficient to reduce viability in the majority of cell lines and primary leukemia samples tested. Therefore, a method was sought to increase steady-state C_{min} concentrations in humans to 1 µM or above. Given the saturated exposure achieved with QD dosing, we utilized a physiological-based PK model to determine the potential reasons for the plateau in the QD schedule. This model indicated that pH-dependent drug solubility was likely the limiting factor and that BID dosing should overcome this plateau, resulting in higher exposures.

The 45 mg BID regimen roughly doubled the exposure relative to the 40 to 65 mg QD average, achieving steady-state C_{min} and C_{max} of 1.5 and 1.8 µM, respectively. One PR was observed in a patient with FL, with what appeared to be a rapid (within 1 week) onset of palpable tumor reduction. Another patient with CLL experienced rapid lymphocytosis, whereas a refractory FL patient demonstrated stable disease. This exposure level, however, resulted in 2 DLTs: 1 patient experienced pancreatitis within 2 weeks of dosing, and a second experienced Grade 3 fatigue. Therefore, it was determined that the exposure range was not tolerated. Of note, the 2 patients with DLT did not achieve the highest exposures at this dose level. We, therefore, aggregated all data from the escalation study to explore PK/AE relationships.

The major difference in exposure between tolerated (40-65 mg QD) and non-tolerated (45 mg BID) doses was the C_{min}, increasing from 0.8 µM to 1.5 µM (steady-state C_{min} by dose level is summarized in Figure 2). Therefore, we explored the relationship between incidences of all treatment-related Grade ≥ 3 AEs with steady-state C_{min}. No relationship was observed up to 1.25 µM steady-state C_{min}. However, above this concentration, there appeared to be some evidence (in the limited number of patients) for increased incidence of Grade 3 AEs (Figure 3). In the context of tumor response, we have observed more consistent anti-tumor activity in the 0.75 to 1.25 µM steady-state C_{min} concentration range, including 3 patients achieving PR (Figure 4). Hence, it appears that steady-state C_{min} of 0.75 to 1.25 µM is likely to be efficacious and well tolerated. Furthermore, our dosing experience thus far indicates that a more consistent steady-state C_{min} is obtained across patients with BID dosing. Thus, under Amendment 4 we recommended a 35 mg BID dosing schedule that targets steady-state C_{min} within the range of

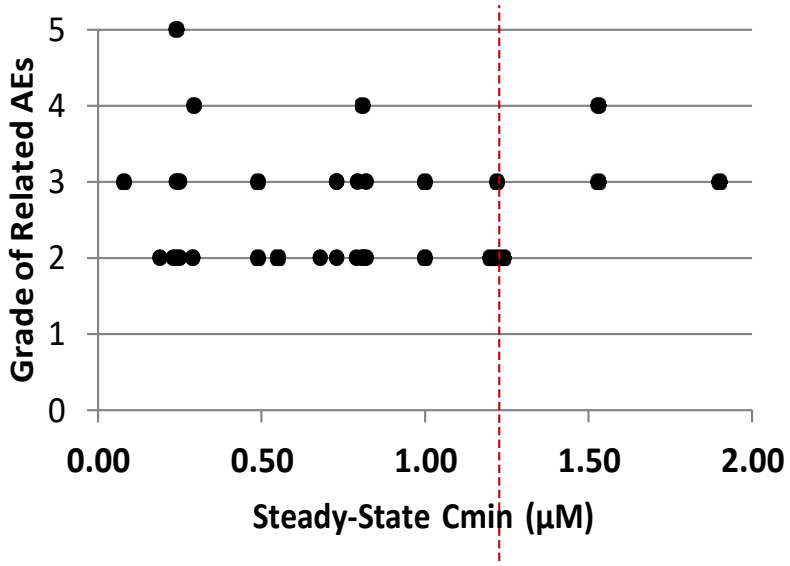
0.75 to 1.25 µM. Following an initial safety review of 12 patients dosed in the Phase 2a study, it was observed that whereas the majority of patients did achieve steady-state C_{min} in the desired exposure range, 3 patients (25%) continued to accumulate plasma exposure to drug beyond Day 8 (the expected time to steady-state); this resulted in exposures greater than originally modeled from the data gathered during once-daily dosing (i.e., in the 2-4 µM range and exceeded the modeled C_{max} target by 1.5- to 2.5-fold). Of these 3 patients, 2 experienced Grade 5 infections (i.e., with fatal outcomes), and 1 patient experienced Grade 3 chemical pancreatitis. Although causality between cerdulatinib exposure and the observed SAEs cannot be determined, as of Amendment 5 the starting dose was lowered from 35 mg BID to 30 mg BID to correct for this unexpected accumulation in cerdulatinib exposure and to provide an extra margin of safety for patients.

Figure 2: Individual Trough Levels (C_{min}) for Tolerated (40-65 mg QD) and Non-tolerated (45 mg BID) Dose Regimens of Cerdulatinib on Day 29 (First Day of Cycle 2)



BID = Twice daily; C_{min} = Minimum concentration (i.e., trough level); PK = Pharmacokinetic; QD = Once daily
Notes: Individual trough (pre-dose) concentrations are shown for patients on Day 29, the first day of Cycle 2. The horizontal bar is the mean value and the longitudinal bar shows the range for each dose cohort. The PK-modeled estimates for trough (C_{min}) concentrations are shown as dashed lines for reference purposes. The predicted mean for the 45 mg BID dose is very close to the actual mean value. The QD dose cohorts of 40, 45, 50, and 65 mg had mean values close to the predicted C_{min} for 30 mg BID. The predicted C_{min} level for the 35 mg BID schedule is slightly higher, and if tolerated, should provide the best opportunity to minimize variability and increase the number of observed responses.

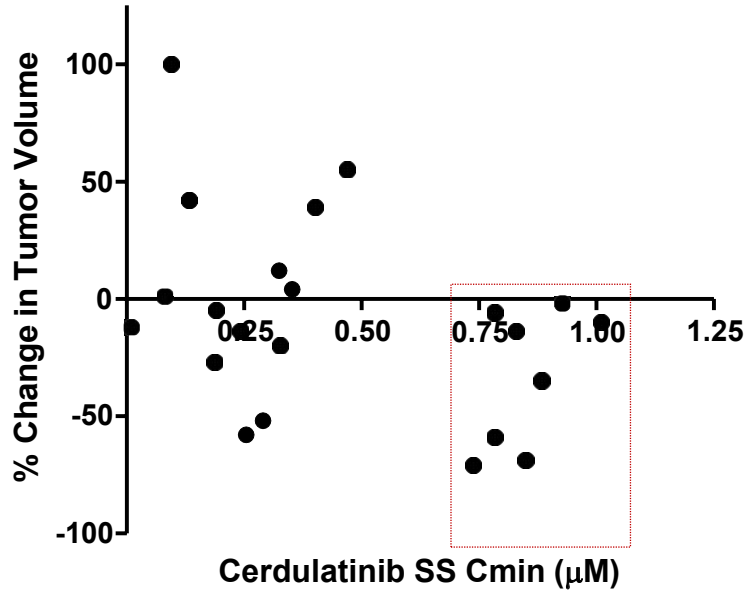
Figure 3: Steady-State Cerdulatinib Plasma Concentrations and Treatment-related Grade 2 + Adverse Events



AE = Adverse event; C_{min} = Minimum concentration (i.e., trough level)

Notes: Treatment-related Grade 2+ AEs are shown on y-axis, with steady-state cerdulatinib plasma concentration at C_{min} on the x-axis. The red dashed line depicts the exposure (~1.25 µM) at which there may be a concentration-effect on AE profile.

Figure 4: Change in Sum of Tumor Volumes from Computed Tomography Scans



C_{min} = Minimum concentration (i.e., trough level); CT = Computed tomography; SS = Steady state

Notes: The best percent change in sum of tumor volumes from CT scans is shown on the y-axis. Cerdulatinib steady-state plasma concentrations at C_{min} are on the x-axis. The red dashed box highlights the greater consistency in anti-tumor activity in the 0.75-1 µM range.

An estimate of cerdulatinib concentrations from PK modeling for the proposed doses is detailed in Table 7.

Table 7: Estimated Concentrations of Twice Daily (BID) Doses from PK Modeling

BID Dose (mg)	C_{min} (µM)	C_{max} (µM)	C_{ave} (µM)
20 [a]	0.38 ± 0.02	0.89 ± 0.16	0.52 ± 0.09
25	0.66	0.89	0.75
30	0.83	1.09	1.0
35 [a]	1.06 ± 0.50	1.26 ± 0.70	NA
45	1.43	1.78	1.6

BID = Twice daily; C_{ave} = Average concentration; C_{max} = Maximum concentration; C_{min} = Minimum concentration (i.e., trough level); PK = Pharmacokinetic

[a] Observed concentrations.

A PK model was developed to estimate steady-state concentration for BID dosing. This model used the average steady-state concentrations for previous BID dose cohorts at dose levels 15, 20, and 45 mg. In addition, the plasma concentrations from the patient who received 30 mg BID as part of a dose reduction was included in the model. The model incorporated the saturated clearance previously observed for cerdulatinib. The results are consistent with the data obtained to date for the 45 mg BID dose and are close to that observed with the single patient who received 30 mg BID.

3.1.2.2.2. Rationale for Individual Dose Titration in Phase 2a

Given the variability of cerdulatinib levels investigated to date, it is possible that some patients may be able to tolerate higher doses of cerdulatinib than others. Therefore, under Amendment 4 patients were allowed to escalate to 40 mg BID after undergoing one 28-day cycle without Grade 3 or higher clinically significant toxicity. In addition, modeling data in Table 7 suggested that this dose regimen would provide C_{min} in the acceptable range of between 0.75 and 1.25 µM. As shown in the literature, this dose titration approach based on clinical tolerability has been used with other tyrosine kinase inhibitors, and patients who tolerated the higher doses often achieved higher response rates [72]. However given the SAEs observed in the first 12 patients dosed at 35 mg BID (the starting dose under Amendment 4), both the starting dose and dose titration strategy were modified. The starting doses are 30, 25, or 20 mg BID.

Dose reductions and subsequent dose escalations back to a maximum dose of 30 mg BID may be permitted per the Dose Modification Guidelines for Phase 2a (Section 5.2.1.3). As indicated in Table 6, the dose reductions are expected to lower overall exposure in a step-wise fashion. The dose of 20 mg BID was studied in 3 patients in the Phase 1 portion of this study and was well tolerated.

3.1.3. End of Study

The end of study will occur when all patients have completed the follow-up visit at 30 days post-treatment, or until all patients have died, have been discontinued (under advice of the physician, at the request of the Sponsor), have withdrawn consent, or are lost to follow-up, whichever occurs first.

3.1.4. Total Number of Patients, Cessation of Treatment, and Total Duration of the Study

Under Phase 1 (closed to enrollment), 52 patients were enrolled, and 43 were dosed. Under Phase 2a, approximately 240 patients can be enrolled. Thus, a total of up to 283 patients can be dosed in the study.

Patients enrolled under Phase 1 and Phase 2a may continue to receive cerdulatinib or cerdulatinib in combination with rituximab (in the combination cohort No. 2; see Table 6) in the absence of disease progression or intolerable toxicity, until they meet any other withdrawal criteria, (Section 4.4) or until the end of study (defined in Section 3.1.3).

The total duration of the study is expected to be approximately 6 years.

3.1.5. Assessments

Safety will be monitored by serial physical exams, vital signs, hematology, and chemistry laboratory studies, and by reported AEs.

Blood samples will be obtained at frequent intervals for determination of cerdulatinib concentration.

Serum will be obtained for analysis of the PD effects of cerdulatinib.

Antitumor activity will be assessed every 8 to 12 weeks according to the revised International Working Group (IWG) criteria [3] or the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria [2].

3.2. Randomization and Blinding

This is an open-label, unblinded study.

4.0 SELECTION, ENROLLMENT, AND WITHDRAWAL OF PATIENTS

During the Phase 1 portion (now closed to enrollment), the study was conducted in patients with relapsed or refractory CLL/SLL or B-cell NHL. During the Phase 2a portion, the study will be conducted in patients with various B- and T-cell NHL (see Section 3.1.2 for the rationale for including patients with T-cell malignancies).

4.1. Inclusion Criteria

4.1.1. Phase 2a Cancer-specific Inclusion Criteria

1. Patient must have a histologically confirmed diagnosis of 1 of the following:
   - (Note: Definitions for "relapsed" and "refractory" disease are provided in Table 3).
   - FL Grade 1 to 3A, with relapsed or refractory disease.
   - Aggressive NHL (aNHL) defined as DLBCL, FL Grade 3B, MCL, and transformed NHL with relapsed disease, relapsed and refractory after 1 to 3 prior chemotherapy regimens.
   - CLL/SLL, with relapsed or refractory disease.
   - PTCL, with relapsed or refractory disease.
   - CTCL with relapsed or refractory disease. Only CTCL patients with MF/SS are allowed.

Patients who received any BCR pathway inhibitor (e.g., BTK inhibitors such as ibrutinib, or PI3 Kinase inhibitors such as idelalisib) and/or BCL2 pathway inhibitors (e.g., venetoclax), and were either intolerant to therapy or had relapsed/refractory disease following therapy are also eligible.

4.1.2. Phase 2a General Inclusion Criteria

1. Patient must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 or 1.
2. Patient must be 18 years or older, of either sex, and of any race.
3. Patient (and/or parent/guardian for patients who otherwise are unable to provide independent consent) must be willing to give written informed consent and be able to adhere to dose and visit schedules.
4. Patient has had prior treatment for lymphoid malignancy requiring treatment for progressive disease/refractory disease (per guidelines for diagnosis and treatment of CLL [2] and revised response criteria for malignant lymphoma [3]).
5. Patient has had ≥ 1 prior systemic treatment regimen administered for at least 2 cycles (unless the patient was intolerant or experienced documented progression on therapy) that must have involved either: 1) an anti-CD20 agent (such as rituximab) WITH chemotherapy for B-cell NHL, unless contraindicated in the judgement of the investigator

(e.g., the patient was not a candidate for chemotherapy and received ibrutinib as first-line treatment); 2) a cytotoxic chemotherapy drug for T-cell NHL; 3) an anti-CD20 agent (such as rituximab) with chemotherapy for CLL, unless contraindicated in the judgement of the investigator (e.g., the patient was not a candidate for chemotherapy and received ibrutinib as first-line treatment); or 4) in patients with CD30-expressing PTCL, a CD30-directed antibody (e.g., brentuximab vedotin).

6. Female patients of childbearing potential and male patients must agree to abstain from sexual intercourse or to use an effective method of contraception during the study and for 90 days following the last dose of protocol therapy (examples of effective methods of contraception include oral contraceptives or double barrier methods such as condom plus spermicide or condom plus diaphragm). Patients enrolled into Cohort 2 should use effective contraception during treatment with rituximab and for 12 months after the last dose of rituximab.
7. Patient must have adequate bone marrow reserve as evidenced by an absolute neutrophil count (ANC) ≥ 1,000/μL, platelet count ≥ 75,000/μL. Platelet count must be without transfusion support within 7 days of the first dose of cerdulatinib.

   Note: CLL patients only: ANC ≥ 750/μL and platelet count ≥ 30,000/μL are acceptable. There are no limits on ANC or platelet count required for patients with leukemic forms of PTCL (ATLL, PLL, LGL) or HSTCL as long as cytopenia, if present, is secondary to disease.
8. Patient must have adequate renal function as evidenced by a creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault equation or based on a 24-hour urine specimen).
9. Patient must have adequate hepatic function as evidenced by a serum bilirubin level ≤ 2.0 mg/dL AND serum AST/ALT levels ≤ 2.5× the ULN for the reference lab. Serum bilirubin ≤ 2.5 mg/dL when increase clearly documented as due to Gilbert's syndrome.
10. Where available, ability to submit a formalin-fixed paraffin embedded tissue (FFPE) block or a minimum of 10 unstained, freshly cut FFPE tissue slides from lymph node or other biopsies that were collected as part of patient diagnosis. If samples are unavailable the patient is still eligible for enrollment.
11. Measureable disease for a given tumor type, defined as:
    a. The presence of ≥ 1 lesion that measures ≥ 1.5 cm in a single dimension as assessed by CT, CT/PET for patients with nodal or mass lesions (e.g., FL, DLBCL, other NHL), or
    b. Quantifiable circulating tumor cells for patients with circulating tumor (e.g., Sézary Syndrome [SS]), or
    c. For CTCL: mSWAT score > 0.

12. Ability to provide redacted copies of pathology reports and radiology reports used for the diagnosis of NHL or CLL. In addition, for CTCL, ability to provide redacted photographs of skin responses.

4.1.3. Phase 2a Cohort-specific Inclusion Criteria

4.1.3.1. Cohort 1 (FL) – Grades 1 to 3A (Single-agent Cerdulatinib)

1. Received ≥ 1 prior treatment regimen.

4.1.3.2. Cohort 2 (Combination) – FL, Grades 1 to 3A (Cerdulatinib + Rituximab)

1. Received ≥ 1 prior treatment regimen.

4.1.3.3. Cohort 3 (aNHL) – aNHL (Single-agent Cerdulatinib)

Aggressive non-Hodgkin lymphoma (aNHL) is defined as DLBCL, FL Grade 3B, Mantle Cell Lymphoma (MCL), and transformed NHL.

1. Relapsed from ≥ 1 but ≤ 3 prior cytotoxic chemotherapy regimens with an anti CD20 antibody, (e.g., R-CHOP, BR). Patients must have received an anthracycline based therapy unless anthracyclines were deemed inappropriate in the judgement of the investigator. Patients must have either relapsed following autologous stem cell therapy (ASCT), or not be candidates (ineligible) for ASCT, defined as meeting any of the following criteria [1]:
   a. Age ≥ 70 years.
   b. Carbon monoxide diffusion capacity (DLCO) < 50% by pulmonary function tests.
   c. Forced expiratory volume in 1 second/forced vital capacity FEV_1/FVC < 60% predicted by pulmonary function tests.
   d. Left ventricular ejection fraction (LVEF) < 45% by multiple gated acquisition (MUGA) or echocardiogram.
   e. Uncontrolled arrhythmia.
   f. Calculated creatinine clearance (Cockcroft-Gault) ≤ 60 mL/min.
   g. Other comorbidities (e.g., medical conditions or psychosocial conditions) that would likely result in an unacceptably high probability of treatment/transplant related morbidity and mortality in the judgement of the investigator (e.g., high Hematopoietic Cell Transplantation Co-Morbidity Index [HCT-CI], Cumulative Illness Rating Scale [CIRS] scores).
   h. Refusal of ASCT.

   Note: Antibody drug conjugates (ADC) count as cytotoxic chemotherapy. Salvage chemotherapy prior to ASCT with or without maintenance therapy counts as one regimen.

4.1.3.4. Cohort 4 (CLL/SLL) – CLL/SLL (Single-agent Cerdulatinib)

1. Received ≥ 1 prior treatment regimen.

4.1.3.5. Cohort 5 (PTCL NHL) – Peripheral T-cell NHL (PTCL) (Single-agent Cerdulatinib)

1. Received ≥ 1 prior systemic treatment regimen for PTCL. In patients with CD30-expressing PTCL, prior treatment must include a CD30-directed antibody (e.g., brentuximab vedotin).

4.1.3.6. Cohort 6 (CTCL NHL)– Cutaneous T-cell NHL (CTCL, MF/SS only) (Single-agent Cerdulatinib)

1. Received ≥ 1 prior systemic treatment regimen for CTCL.

4.2. Phase 1 and Phase 2a Exclusion Criteria

A patient meeting any 1 of the Exclusion Criteria listed below will be excluded from the trial.

1. Patient has Richter's syndrome, Burkitt's lymphoma, or Burkitt-like Lymphoma. Patients with transformed DLBCL from Follicular NHL are eligible.
2. Patient has undergone prior allogeneic or autologous transplant with infusion of stem cells within 90 days before Cycle 1 Day 1 (C1D1), or on active immunosuppressive therapy for graft-versus-host disease (GVHD) or GVHD prophylaxis within 8 weeks before C1D1.
3. Patient has received prior therapy with a spleen tyrosine kinase (SYK) inhibitor.
4. Patient requires chronic treatment with a strong CYP3A4 inhibitor or inducer or CYP3A4-sensitive substrate (Appendix 3).
5. Patient has known lymphomatous involvement of the central nervous system (CNS).
6. Patient has a known hypersensitivity to any of the components of cerdulatinib.
7. Patient has persistent, unresolved NCI-CTCAE v5.0 ≥ Grade 2 clinically significant (in the judgement of the investigator) drug-related toxicity (except alopecia, erectile impotence, hot flashes, libido, neuropathy) associated with previous treatment.
8. Prior monoclonal antibody (mAb) (including alemtuzumab), radioimmunoconjugate, antibody drug conjugate (ADC), phototherapy, radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 3 weeks before Cycle 1 Day 1.
9. For CTCL patients only: total skin electron beam therapy (TSEBT) within 12 weeks, or initiation of topical steroid, nitrogen mustard, or topical retinoid within 2 weeks before Cycle 1 Day 1. Patients with CTCL who are on a stable topical regimen for ≥ 4 weeks prior to C1D1 are allowed.

10. The patient has a known infection with HIV, HBV, or HCV or is a carrier of HBV or HCV. Patients who are seropositive for HCV antibody must test negative for HCV by PCR assay to be eligible. Patients with an occult or prior HBV infection (defined as being seropositive total hepatitis B core antibody [HBcAb] and seronegative for HBsAg) may be included if his or her HBV DNA is undetectable or if it is undetectable with antiviral therapy. These patients must be willing to undergo additional testing per local standard of care if this data is unavailable. Additional testing will be performed if the patient does not have documentation of a negative hepatitis panel and a negative HIV history within the 12-week period prior to enrollment.
11. Patient has an active infection requiring systemic treatment, defined as requiring antimicrobial, antifungal, or antiviral agents. Prophylactic antimicrobial treatment is permitted.
12. Patient has significant gastrointestinal disease that may interfere with absorption of the study drug or that predisposes him/her to GI adverse effects, or has had major gastric or bowel surgery.
13. Patient has difficulty swallowing or malabsorption syndrome.
14. Patient has any other medical, social, or psychiatric condition that might interfere with the patient's participation in the trial or interfere with the interpretation of trial results.
15. Patient has undergone major surgery within 4 weeks prior to first study drug administration.
16. Patient has a history (within 2 years prior to first study drug administration) of another malignancy unless malignancy treated with curative intent and likelihood of relapse is small (< 5% in 2 years in the judgement of the investigator). Patients with a history of squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix may be enrolled.
17. Patient is receiving systemic steroids at doses greater than the equivalent of prednisone, 20 mg daily, with the exception of intermittent use for the treatment of emesis.
18. Patient is female and is breast-feeding, pregnant, or intends to become pregnant.
19. Patient is participating in any other therapeutic clinical study (observational or registry trials are allowed).

4.3. Enrollment Process

After informed consent is obtained, the required screening procedures are performed, and the results known, the site PI/designee will complete the enrollment form and send it to the Sponsor/designee, along with supporting documentation as listed in the study manual. After Sponsor/designee review, if eligible, the Sponsor/designee will assign a patient study number to the patient and inform the site PI/designee.

4.4. Withdrawal Criteria and Replacement of Patients

Patients are free to withdraw from the study at any time for any reason; however, to the extent possible, all patients should continue to participate in the study once they have enrolled, even if they discontinue study drug. The Investigator also has the right to withdraw a patient from the study in case of events such as inter-current illness, AEs, progression, protocol violation, other procedures needed for treatment of their disease, or other medical conditions, administrative reasons or for other reasons (detailed in Section 4.4.1).

An excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. Reasons for all discontinuation of study drug and withdrawals from the study will be recorded. If a patient discontinues the study drug due to an AE, that AE must be evaluated to determine if it is a serious adverse event (SAE; see Section 10.1.2). The Investigator must report all SAEs to the Syneos Safety Department (the Sponsor's Safety Designee) on the SAE form within 24 hours from the point in time when the Investigator becomes aware of the SAE. The procedures described under 30 Days Post-Last Treatment (Section 7.3.2.2) will be performed upon discontinuation/withdrawal, whenever possible. If a patient withdraws consent, no further information will be collected after the study termination visit.

Normal study termination is defined as the 30 Days Post-Last Treatment visit in Section 7.3.2.2.

4.4.1. General Withdrawal Criteria

Discontinuation of study drug and/or withdrawal from the study will occur if any of the following apply:

- The patient experiences disease progression requiring other therapy.
- The patient develops intolerable toxicity.
- The patient develops an intercurrent condition precluding further administration of cerdulatinib.
- The patient withdraws consent for further participation in the trial.
- The patient becomes pregnant.
- The patient fails to comply with study drug administration, dosing evaluations, or other requirements of the study.
- The patient needs a concomitant medication that makes the patient ineligible for further participation in the study.
- The Investigator believes it is no longer in the best interest of the patient to receive cerdulatinib.
- The Sponsor discontinues the trial.

4.4.2. Specific Withdrawal Criterion and Replacement Procedure for Phase 1

- Patients who discontinue from treatment prior to the completion of Cycle 1 or who do not receive at least 80% of the intended dose in Cycle 1 for reasons other than toxicity will be replaced. Dose escalation will not take place until the appropriate number of patients has completed Cycle 1 at the designated dose level.

4.4.3. Specific Withdrawal Criteria and Replacement Procedure for Phase 2a

- Patients who do not have at least 1 post baseline assessment for efficacy will be withdrawn from the study and may be replaced.
- Patients who are found to have protocol violations that substantially impair the evaluation of safety and efficacy may be replaced.

4.5. Withdrawal and/or Replacement Criteria for Site or Principal Investigator

The site or Principal Investigator may be withdrawn or replaced from the study due to poor compliance with the study protocol or poor accrual.

4.6. Sponsor Study Discontinuation

The Sponsor has the right to terminate the entire study or study cohorts at any time. Reasons for terminating the study or study cohorts may include, but are not limited to, the following:

- Excessive toxicity indicating a potential health hazard to patients.
- Poor patient enrollment.

The Sponsor will notify the Investigator if the study is placed on hold (or if individual cohorts are placed on hold), or if the Sponsor decides to discontinue the study or program.

4.7 Protocol Violations and Deviations

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following categories:

- Enrollment criteria.
- Study activities (e.g., missed evaluations or visits, data verification issues).
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay, or discontinuation criteria.
- Investigational product handling, including storage and accountability.
- Informed consent and ethical issues.

5.0 TREATMENTS ADMINISTERED

Treatments administered during the study are listed below. Administration of study drug and related dose modifications are described in Sections 5.1 and 5.2 for cerdulatinib and in Section 6.2 for rituximab.

- Phase 1 (**closed**): single-agent cerdulatinib
- Phase 2a:
  - Cohorts 1, 3, 4, 5, and 6: single-agent cerdulatinib
  - Cohort 2: cerdulatinib and rituximab

5.1. Cerdulatinib Study Drug Administration

5.1.1. General Instructions

Cerdulatinib may be taken with food, unless otherwise specified. Missed doses may be made up if given within 4 hours of the missed scheduled dosing time. Cerdulatinib may not be taken fewer than 8 hours prior to the next scheduled dose. Patients who vomit following administration of cerdulatinib should not repeat that dose of cerdulatinib but should resume study drug with the next scheduled dose. In the event of toxicity, dosing may be interrupted at the discretion of the treating physician until sufficient resolution of the toxicity is attained and then may be restarted at a lower dose level (see Section 5.2 for guidelines for cerdulatinib toxicity and subsequent dose modifications).

In order to assess cerdulatinib compliance, patients will be instructed to keep patient diaries to document self-administration of study drug doses, and will include documentation of time study dose was taken, any missed doses and reason(s) why missed, and/or any wasted doses and reason(s) why. The diary will be reviewed by the appropriate study staff during study visits.

5.1.2. Phase 1 Cerdulatinib Dosing

5.1.2.1. Initial Dosing with Cerdulatinib

Following screening and confirmation of eligibility, patients will be sequentially assigned to the next open dose cohort. For QD dosing regimens, to allow for single-dose PK assessments during the Phase 1 portion of the study, patients will take their first dose of cerdulatinib on Day 1 and their second and subsequent doses daily beginning on Day 4. During Part 1 of the study, cerdulatinib will be taken orally once daily in the AM. For BID dosing regimens, BID dosing can begin on Day 1.

The initial dose cohort will begin treatment at a dose of 15 mg po QD. Subsequent total daily dose levels that may be studied include 30 mg, 60 mg, 90 mg, 120 mg, and 150 mg daily. Intermediate or higher dose levels may be studied, as appropriate, given the safety and PK profiles of cerdulatinib observed during the ongoing conduct of this study. Depending on the

PK profile, twice-daily administration (BID) may be considered during the course of dose escalation. Single-dose PK assessment will not be conducted for BID cohorts. Increments of dose escalation will be adjusted as needed to accommodate available capsule strengths. Every effort should be made to administer study drug at the same times each day.

Patients who do not receive at least 80% of their cerdulatinib doses in the first 28 days of treatment (Cycle 1) due to non-compliance will be withdrawn from the study. Beyond Cycle 1, dose holds may be permitted for reasons not related to disease progression or drug-related toxicity (e.g., elective procedures, vacations) with the permission of the Sponsor's Medical Monitor.

Intra-patient dose escalation will not be permitted during Phase 1.

The dose-escalation scheme described in this and the following paragraph accords with the principles described by Le Tourneau et al [6]. One patient will be enrolled in each dose cohort until the first report of a Grade 2 or greater adverse event (AE). In the event of any Grade 2 or greater AE in the single patient, an additional 2 patients, for a total of 3, will be enrolled in that dose cohort, and all subsequent dose cohorts will follow a "3 + 3" design. Dose escalation will be in 100% increments until a drug-related adverse event of Grade 2 or greater severity occurs. Thereafter, dose escalation will be in increments of up to 50% as determined following review by the safety committee. If a dose-limiting toxicity (DLT) occurs in 1 of the first 3 patients in a cohort, that cohort will be expanded to at least 6 patients. If ≤ 33% of six or more patients in a cohort experiences DLT, dose escalation may proceed. If in any cohort 2 or more of the first 3 patients or ≥ 33% of patients in a cohort develop DLT, dose escalation will cease. That dose level will be declared intolerable, and either the prior dose level will be declared the MTD, and/or the cohort may be expanded to as many as 6 patients if fewer than 6 patients had previously been treated at that dose level in order to further characterize the PK and PD at that level. A total of 43 patients have been enrolled in the Phase 1 (escalation) portion of this study, and Phase 1 is now closed to enrollment.

All patients in a cohort must have been treated for 28 days (one cycle) prior to treatment of patients at the next higher dose level. In addition to DLTs defined below, the safety committee will also take into consideration the totality of available safety data in determining whether a given dose level should be deemed tolerable. Additional patients may be enrolled in individual cohorts if the Sponsor's Medical Monitor or safety committee deems it necessary to obtain additional safety information prior to proceeding with dose escalation. In addition, intermediate dose levels may be used to allow for further exploration of safety.

As of Amendment 4, Phase 1 dose escalation has concluded at 45 mg po BID (per Sections 1.5 and 3.1.2.2). The dose selected for Phase 2a is 35 mg po BID based on PK modeling and accumulated safety data (Section 3.1.2.2).

5.1.3. Phase 2a Cerdulatinib Dosing

Following confirmation of eligibility, patients will receive oral cerdulatinib at a starting dose of 30, 25, or 20 mg BID. Every effort should be made to administer study drug at the same time each day. The drug will be administered in cycles of 28 days with no days off therapy between cycles.

In the event of toxicity (see Section 5.2.1 for the definition of *toxicity*), dosing may be interrupted at the discretion of the Investigator until sufficient resolution of the toxicity is attained and then restarted at a lower dose level (dose modifications to cerdulatinib are summarized in Table 8). The lowest dose of cerdulatinib that may be administered is 15 mg BID.

Dosing information for rituximab is described in Section 6.2 (for Cohort 2, the combination cohort of cerdulatinib and rituximab).

5.2. Dose-limiting Toxicity, Dose Modifications, and other Dosing/Monitoring Guidance

5.2.1. Cerdulatinib

5.2.1.1. Definitions of Dose-limiting Toxicity for Cerdulatinib during Phase 1

DLT will be defined as any of the following toxicities, possibly or probably related to cerdulatinib, and clinically significant (in the judgement of the investigator) that occurs in the first 28 days (one cycle) of treatment. For patients to be evaluable for DLT, they must have received 80% of the doses in the first 28 days of Cycle 1, or been withdrawn from study therapy due to a drug-related toxicity. Patients who withdraw without meeting these criteria should be replaced. Toxicity will be graded according to the NCI-CTCAE v4.0.

Hematologic

- Febrile neutropenia (ANC < 1,000/μL and temperature ≥ 38.5°C).
- Grade 4 neutropenia for > 5 days.
- Grade 4 thrombocytopenia with or without bleeding.
- Grade 3 thrombocytopenia with bleeding.
- Grade 4 anemia, unexplained by underlying disease.

Non-hematologic

- Grade 3 or greater nausea, vomiting, or diarrhea if persistent despite optimal antiemetic or anti-diarrheal therapy.

- Grade 3 or greater increase in transaminases lasting > 5 days.
- Grade 3 or greater fatigue persisting > 7 days in the absence of any other underlying cause.
- Any other Grade 3 or greater non-hematologic toxicity (except fatigue as noted above) considered clinically significant by the investigator.
- Toxicity of any grade resulting in dose delay of more than 7 days.
- Toxicity resulting in study drug discontinuation prior to the completion of Cycle 1.

5.2.1.2. Phase 2a: Monitoring for Toxicity in Phase 2a

Patients will be monitored for toxicity throughout Phase 2a. For the purposes of this protocol, toxicity is defined as any Grade 3 or higher adverse event (AE) and/or any clinically significant AE (refer to Table 8). Patients experiencing a toxicity may be considered for a dose interruption or reduction. Enrollment in a cohort may be suspended at any time depending on the overall toxicity profile within that cohort, pending a review by the Study Committee, and consideration will be given to discontinuing enrollment in that cohort or providing a global dose reduction for that cohort.

Physicians should monitor for infections and clinically significant decreases in leukocyte counts (e.g., ALC, ANC) and should consider holding cerdulatinib and/or dose modifications per Section 5.2.1.3 if clinically significant toxicity occurs. Also see Section 10.1.3, Adverse Events that May Indicate Potential Drug Toxicity.

5.2.1.3. Dose Modifications for Cerdulatinib

5.2.1.3.1. Dose Modifications to Cerdulatinib During Phase 2a

Dose reductions and interruptions are permitted during all cycles. Guidelines for dose modifications are provided in Table 8.

In general, for Grade 1 or 2 adverse events that are medically manageable, the Investigator is encouraged to continue dosing and institute standard of care support or hold dosing and institute standard of care support, and then restart dosing at the same dose after the event has resolved to baseline. Specific guidance for management of Grade 1 and 2 diarrhea and nausea and vomiting is provided in Sections 5.2.1.5 and 5.2.1.6.

For adverse events ≥ Grade 3, rather than dose interruption or dose reduction, the Investigator is encouraged to hold dosing and institute standard of care support, and then restart dosing at the same dose after the event has resolved to baseline, as clinically appropriate. Table 8 provides further guidance on Grade 3 toxicities. A dose interruption does not necessitate a subsequent dose reduction. In the case of a dose interruption, once the toxicity has resolved to Grade < 2 or

baseline, the Investigator should use clinical judgement when deciding to restart the patient at the same dose level or at a reduced dose.

Patients may be dose-reduced in increments from their starting dose, one level at a time, to the lowest dose level of 15 mg BID. A patient experiencing a toxicity at 15 mg BID should be discontinued from cerdulatinib and removed from the study (after completing the 30 Day Post-Last Treatment Visit in Section 7.3.2.2).

Patients who experience dose interruptions > 28 days in duration should be permanently discontinued from cerdulatinib therapy (after completing the 30 Day Post-Last Treatment Visit in Section 7.3.2.2). Exceptions that would allow such patients to continue study treatment may be allowed at the discretion of the Investigator based upon clinical judgement and with Sponsor Medical Monitor approval.

5.2.1.3.2. Dose Re-escalations During Phase 2a

In Phase 2a, a patient who has been dose reduced from their starting dose may be re-escalated incrementally to the next higher dose level at the discretion of the Investigator based upon clinical judgement and with Sponsor Medical Monitor approval. Dose re-escalation to the next higher dose level should occur at the start of the next cycle.

Table 8: Guidelines for Dose Reductions for Cerdulatinib

Toxicity	Occurrence	Action [1]
Hematologic Grade 3 or 4 febrile neutropenia Grade 4 neutropenia for ≥ 7 days, or Grade 4 thrombocytopenia	1st	Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, may restart cerdulatinib at the next lower dose level.
	2nd	Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, may restart cerdulatinib at two dose levels below the starting dose.
	3rd	Discontinue cerdulatinib
Gastrointestinal Grade 3 or 4 nausea, vomiting, or diarrhea if persistent despite optimal antiemetic or antidiarrheal therapy Grade 3 or greater increase in ALT/AST, total bilirubin	1st	Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, may restart cerdulatinib at the next lower dose level.
	2nd	Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, may restart cerdulatinib at two dose levels below the starting dose.
	3rd	Discontinue cerdulatinib
Other Any other related Grade 3 or 4 non-laboratory toxicity Any other related Grade 3 or 4 laboratory toxicity considered clinically significant by the Investigator (e.g., symptomatic) (Do not dose reduce or hold study drug for asyptomomatic amylase or lipase elevations [2])	1st	Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, may restart cerdulatinib at the next lower dose level.
	2nd	Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, may restart cerdulatinib at two dose levels below the starting dose.
	3rd	Discontinue cerdulatinib

AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase

Note: Grading is NCI CTCAE v5.0.

[1] Do not dose reduce below 15 mg BID. At 15 mg BID, if any toxicity (Grade 3 or greater AE and/or any clinically significant AE) occurs, discontinue cerdulatinib (and rituximab for the combination cohort of cerdulatinib and rituximab) after completing the 30 Day Post-Last Treatment Visit in Section 7.3.2.2.

[2] ≥ Grade 3 asymptomomatic elevations in amylase and lipase have been observed in this study without clinical pancreatitis.

5.2.1.4. Management of Potential Epstein-Barr Virus Reactivation

EBV reactivation has been observed in connection with cerdulatinib administration and should be viewed as a potential adverse effect of treatment. For this reason, peripheral blood quantitative EBV polymerase chain reaction assay (PCR) has been added to the baseline assessment of subjects and should be performed post-baseline for any unexplained fevers if there is clinical suspicion of EBV reactivation.

If unexplained fever and increased EBV PCR raise clinical suspicion of EBV reactivation or infection, the investigator should take the following action *:

1. Hold cerdulatinib dosing.
2. Continue monitoring the patient's EBV viral load with quantitative PCR per local standard of care (typically weekly).

3. Administer symptomatic treatment per local standard of care.
4. Consider therapy with rituximab at a dose of 375 mg/m^2 once weekly until normalization of the patient's viral load. Typically, one to four doses of rituximab are used [73, 74]. The use of rituximab does not require study discontinuation.
5. After symptoms resolve, resume cerdulatinib treatment at the same dose level or one dose level below the current dose level and continue monitoring the patient's EBV viral load with quantitative PCR per local standard of care (typically monthly).

* Cerdulatinib dosing may continue while rituximab therapy is administered, with the Medical Monitor approval. For asymptomatic increased EBV PCR, consider treatment with rituximab (per local standard of care) and continuing cerdulatinib.

5.2.1.5. Management of Diarrhea

Grade 1 or 2: The patient may continue receiving study drug. Institute anti-diarrheal treatment (e.g., loperamide [Imodium®] or diphenoxylate/atropine [Lomotil®]) and consider BRAT (bananas, rice, applesauce, and toast) diet. Persistent Grade 2 diarrhea despite optimal therapy may be managed with dose reduction.

Grade ≥ 3: Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, restart cerdulatinib at the same dose level or at the next lower dose level.

Also, if clinically indicated, the patient should be assessed for *C. difficile* infection.

5.2.1.6. Management of Nausea and Vomiting

Grade 1 or 2: The patient may continue receiving study drug. Institute anti-emetic treatment (e.g., ondansetron [Zofran®] or prochlorperazine [Compazine®]), consider sucralfate (Carafate®), and institute standard of care support. Persistent Grade 2 nausea/vomiting despite optimal therapy may be managed with dose reduction.

Grade ≥ 3: Hold study drug. Once toxicity has resolved to Grade < 2 or baseline, restart cerdulatinib at the same dose level or at the next lower dose level.

5.3. Rituximab Information and Dose Modifications

For patients enrolled in Cohort 2, rituximab will be provided as standard of care by the Investigator. Rituximab will not be provided by the Sponsor.

5.3.1. Prescribing Information

Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

5.3.2. Management of Rituximab Infusion Toxicity

Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

5.3.3. Dose Modifications to Rituximab

Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

Escalations and reductions in rituximab dosing are not planned nor permitted. Repeat rituximab administrations may be delayed to allow patients to recover from rituximab-related AEs or intercurrent illness.

6.0 STUDY MATERIALS AND MANAGEMENT

6.1. Cerdulatinib

6.1.1. Identity of Product

Cerdulatinib, an investigational drug, is supplied by Portola Pharmaceuticals, Inc. (Portola), as an immediate release (IR) capsule for oral administration in 2 strengths: 5 mg and 15 mg. Each gelatin capsule will contain cerdulatinib HCl, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, and magnesium stearate. The 5 mg capsules will be size 4 and dark green opaque in color, the 15 mg capsules will be size 4 and Swedish orange opaque in color. The study product will be supplied in 35 capsules/bottle in 60 cc high density polyethylene (HDPE) bottles and should be stored at room temperature.

In Amendment 9, additional drug will be provided in the following new presentations:

Cerdulatinib Dose (mg)	Capsule Size	Capsule Color	Bottle configuration
15	Size 3	Blue opaque	30 capsules/bottle in 40 cc HDPE bottles
20	Size 3	White opaque	
25	Size 2	Swedish orange opaque	

6.1.2. Dispensing and Accountability

The dispensing pharmacist or designated qualified individual will write the date dispensed, dose dispensed, and the patient's identification number or initials on the Drug Accountability Source Documents. All medication supplied will be accounted for on the Drug Accountability Record. All partially used or unused drug supplies will be destroyed at the site in accordance with approved written site procedures, or returned to the drug depot as described in the Study Drug Supply Process Manual. The Investigator will maintain a record of the amount, reason, and dates when unused supplies were either destroyed or returned to Portola. All records will be retained as noted in Section 15.2.

6.1.3. Dose Regimens

Patients will receive cerdulatinib at a starting dose of 30, 25, or 20 mg BID (Section 3.1.2.2). Patients may be dose-reduced to a minimum dose of 15 mg BID (Section 5.2.1.3.1). Missed doses may be made up if given within 4 hours of the scheduled dosing time. Cerdulatinib may not be taken fewer than 8 hours prior to the next scheduled dose. Patients who vomit following administration of cerdulatinib should not repeat that dose of cerdulatinib but should resume study drug with the next scheduled dose.

6.2. Rituximab (for Combination Cohort 2, Rituximab and Cerdulatinib)

6.2.1. Identity of Product

Rituximab is commercially available. Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

6.2.2. Dispensing and Accountability

Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

Acquisition, storage, control, and disposal of rituximab used in the study should be performed according to institutional procedures and policies. The dispensing pharmacist or designated qualified individual will write the lot number, date dispensed, dose/amount dispensed, and the patient's identification number or initials on the Drug Accountability Source Documents. All medication supplied will be accounted for on the Drug Accountability Record. All partially used or unused drug supplies will be destroyed at the site in accordance with approved written site procedures. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Portola. All records will be retained per Section 15.2 of the protocol.

6.2.3. Rituximab Dose Regimen (*Cohort 2 Only*)

6.2.3.1. Premedication and Prophylactic Medication

Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

6.2.3.2. Dose Rationale

Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

6.2.3.3. Dosage

Please refer to local prescribing information for further details on rituximab (e.g., USPI, SmPC).

Cerdulatinib should be taken before the rituximab infusion.

Rituximab will be administered intravenously (IV) in the clinic. Dosing will be based on mg/m^2 of body surface area (BSA). The dose calculation of BSA will be based on the patient's height and actual body weight prior to therapy. After establishment of BSA based on the patient's pretreatment body weight, do not alter the total dose of rituximab for the patient, despite fluctuations in the patient's body weight.

Rituximab will be administered IV at 375 mg/m^2 on Days 1, 8, 15, and 22 of Cycle 1, and during Cycles 4, 6, 8, and 10 on Day 1 only.

7.0 STUDY METHODS

A summary of the patient visits and clinical evaluations for Phase 2a is provided in Appendix 1. Please refer to the Study Laboratory Manual for further instructions on specimen processing and shipping.

7.1. Study Assessments

7.1.1. Informed Consent

Written informed consent for participation in the study must be obtained before performing any study-specific screening procedures. Informed Consent Forms for all consented patients will be maintained at the study site.

7.1.2. Global Health Assessment

The Global Health Assessment should be administered after obtaining informed consent but prior to any other protocol procedures. It should be performed before any protocol-related information is communicated to the patient.

7.1.3. Medical History

Medical history should include previously determined prognostic factors, including (but not limited to):

- Follicular Lymphoma International Prognostic Index (FLIPI)
- International Prognostic Index (IPI) score for NHL
- Mantle Cell International Prognostic Index (MIPI)
- Others (see Appendix 4, Appendix 5, Appendix 6, and Appendix 7)

Medical history should also include a redacted copy of the pathology report and any supporting pathology information, including the original pathology report from the diagnosis (which may include additional mutational analysis by sequencing, FISH, IHC, cytogenetics, etc.) to be available for Sponsor review.

7.1.4. Concomitant Medications

All medications, including over-the-counter preparations, herbals, and vitamins taken within 14 days prior to Day 1 and throughout the study should be recorded. Additional information about prohibited and allowed concomitant medications can be found in Section 7.5.

7.1.5. Physical Examination, Height, and Weight

Physical examinations should include heart, lungs, and abdomen. Height and weight may also be required at certain visits (as defined in Appendix 1). In patients with CLL, the physical exam should include bi-dimensional measurements of all lymph nodes and measurement of spleen size.

7.1.6. Vital Signs

Vital signs (temperature, respiratory rate, blood pressure, and heart rate) should be obtained after at least 5 minutes in the sitting or semi-recumbent position. Vital signs should be obtained pre-dose at the visits defined in Appendix 1.

Vital signs should also be obtained post-dose at the visits defined in Appendix 1 at the following time points:

- Cohorts 1, 3, 4, 5, 6 (cerdulatinib only): obtain vital signs at 1.0 hour post-cerdulatinib administration
- Cohort 2 (cerdulatinib + rituximab) on visits rituximab is administered: obtain additional vital signs at 0.5, 1.0, 2.0, 3.0, and 4.0 hours post-cerdulatinib administration (or per standard of care), and then as clinically indicated.

The window for collection of vital signs is ± 10 minutes.

7.1.7. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status scale can be found in Appendix 2.

7.1.8. Electrocardiogram (ECG)

12-lead ECG will be required for all patients (single tracing acceptable, or triplicate ECGs as clinically indicated).

7.1.9. Local Laboratory Tests and Response Assessments

7.1.9.1. Serum Chemistry, Hematology, Urinalysis, Coagulation, and Pregnancy Tests

Serum chemistry, hematology, urinalysis, and PT/PTT/INR assessments should be performed at the local lab. Urine or serum for pregnancy testing should be performed for women of child-bearing potential only. During Screening, these assessments should be completed within 7 days prior to Day 1. The results should be obtained and reviewed prior to enrollment to confirm eligibility.

- Hematology - hemoglobin, hematocrit, WBC, platelet count, CBC with differential.
- Serum Chemistry - sodium, potassium, chloride, magnesium, CO_2 (HCO_3), glucose, BUN, creatinine, aspartate aminotransferase (AST, i.e., serum glutamic-oxaloacetic transaminase [SGOT]), alanine aminotransferase (ALT, i.e., serum glutamic pyruvic transaminase [SGPT]), lactate dehydrogenase (LDH), total protein, albumin, alkaline phosphatase, calcium, phosphorous, bilirubin, uric acid, amylase, and lipase.
  - Grade 3 or greater increases in ALT or AST require liver function testing to be repeated within 72 hours of initial test.
- Complete urinalysis - urine will be obtained at selected time points for the following laboratory tests: specific gravity, pH, glucose, protein, and hemoglobin.

- Microscopic analysis for urine sediment to be performed as clinically indicated.
- Urinalysis will be analyzed at the local laboratory. Analysis results will be captured on study case report forms (CRF).

- Pregnancy Test - Urine or serum will be obtained at Screening and on Day 1 of all cycles from all female patients of child-bearing potential and analyzed at the local laboratory to determine their pregnancy status.

7.1.9.2. Other Local Labs/Assessments for All Patients

The following additional assessments should also be performed locally for all patients:

- Pre-dose blood sample for C-reactive protein (CRP) and ESR-Westergren.
- Whole blood for Beta-2-microglobulin, lymphocyte subsets, and immunoglobulin levels including:
  - Quantitative immunoglobulins - quantitative levels of IgA, IgE, IgG, and IgM.
  - Lymphocyte subsets - quantitation of absolute numbers (or %) of CD3+, CD4+, CD8+, CD16/56+, and CD19+ by flow cytometry, WBCs, and lymphocyte count.
- CT or CT/PET of chest, abdomen, pelvis, plus any other areas of lymphoma/CLL involvement (within 28 days prior to Day 1) and then as indicated in Appendix 1.
  - Note: for CTCL patients, if baseline scan is negative for nodal/visceral/other disease a repeat CT or CT/PET is not necessary except to confirm CR and may be done as clinically indicated.
  - For all patients, redacted copies of radiology reports should be sent to the Sponsor for review.
  - Copies of scans should be made available to Sponsor upon request.
- Obtain copy of molecular/mutation profile if obtained as standard of care.
  - Examples of molecular/mutation profiles: FoundationOne, Caris, MSKCC IMPACT, or other local or commercial profiles.

7.1.9.3. Other Local Labs/Assessments for Specific Patients

The following additional assessments should be performed locally for specific patients as indicated:

- *For Cohort 4 CLL/SLL patients only*, samples should be obtained at Day 1 for prognostic factor determination including:
  - Cytogenetics (FISH) del(13q), del(11q), del(17p), del(6q)
  - IgVH mutational status; results obtained within 3 months prior to C1D1 are acceptable
  - Zap70

- CD38

- If these tests were completed prior to Screening, the historic results should be recorded in the database within the appropriate eCRF. The tests should then be repeated locally at Day 1.
  - For Cohort 6 CTCL patients only:
    - Skin punch biopsy – 1, ≥ 5 mm punch biopsy of a representative lesion. A biopsy should be obtained from 2 different areas of disease, if possible (e.g., plaque and nodular lesions)
    - Peripheral blood flow cytometry – for assessment of Sézary cells
    - Modified Severity Weighted Assessment Tool (mSWAT)
    - Likert Scale assessment
    - Photographs of skin involvement per local standard of care (SOC)

7.1.10. Central Laboratory Assessments

- Details regarding the central laboratory collection procedures can be found in the Study Laboratory Manual. All post-dose central laboratory samples should be collected 2.0 hours after administration of cerdulatinib unless otherwise specified. Before obtaining lab samples, date and time of patient's last mean should be recorded.

7.1.10.1. Central Laboratory Assessments for All Patients:

- Serum sample for cytokine biomarker analysis.

7.1.11. Pharmacokinetics

Plasma samples for cerdulatinib pharmacokinetic (PK) assessments should be obtained at the time points as indicated in Appendix 1. Serial PK samples will be collected at the following time points:

- Cycle 1 Day 1: pre-dose (i.e., within 60 minutes prior to the dose), and 1, 2, 4, 6, 8, and 24 hours post-dose (collection window is ± 10 minutes, except for the 24-hour post-dose timepoint [± 30 minutes]). Collect the C1D1 24-hour post-dose sample prior to administering the C1D2 dose.
- Cycle 1 Day 8: pre-dose (i.e., within 60 minutes prior to the dose), and 1, 2, 4, 6, 8, and 24 hours post-dose (collection window is ± 10 minutes, except for the 24-hour post-dose timepoint [± 30 minutes]). Collect the C1D8 24-hour post-dose sample prior to administering the C1D9 dose.

If a patient is not dosed at a particular visit but is due to be dosed, a trough PK assessment should still be performed.

7.1.12. Biopsies

7.1.12.1. Bone Marrow Biopsy and Aspiration

For CLL patients only, a bone marrow biopsy and aspiration will be completed before Day 1 (within 6 weeks/42 days prior to Day 1) through the local lab and be repeated as clinically indicated. For all other patients with a history of bone marrow involvement prior to entering the study, a repeat biopsy should be performed to confirm a complete response or as clinically indicated.

7.1.12.2. Skin Punch Biopsy (Cohort 6, CTCL Only)

Skin punch biopsy is mandatory for all patients with CTCL and should be a ≥ 5 mm punch biopsy of a representative lesion. A biopsy should be obtained from 2 different areas of disease if possible (e.g., plaque and nodular lesions). Subsequent biopsies should be from the same general site if possible. At least 10 unstained slides or a FFPE tissue block should be submitted.

7.1.12.3. Optional Biopsies

The following optional biopsies may be obtained from all patients at the discretion of the Investigator or as clinically indicated:

- Optional tumor Block/Unstained Slides (Screening) – During Screening, obtain tumor block/unstained slides that were previously collected as part of patient diagnosis if consent given (in selected patients, once eligibility is confirmed). A minimum of 10 (preferably 20) unstained slides or Formalin-fixed paraffin embedded tissue (FFPE) block should be sent to Portola. A fresh tumor biopsy is not required; archival tissue may be used.
- Optional Fresh Tumor Biopsy (Any time during study) – obtain a fresh lymph node or tumor biopsy. Submit a formalin-fixed paraffin embedded tissue (FFPE) block or a minimum of 10 (preferably 20) unstained, freshly cut FFPE tissue slides from lymph node or other biopsies.

If tumor or lymph node or skin biopsies (including CTCL patients) are obtained during the course of the patient's treatment, redacted copies of the pathology reports should be sent to the Sponsor for review. Biopsy processing instructions can be found in the Study Laboratory Manual.

7.2. Screening Visit

All screening assessments will be conducted within 21 days prior to the first dose of study drug. Redacted copies of pathology reports used for the diagnosis of NHL or CLL/SLL, or other documents noted in the enrollment form, should be obtained during Screening.

Additionally, the patient's pathology reports used to make the original diagnosis or diagnosis of relapse/progression should be examined to determine if the markers below were assessed:

- For patients with DLBCL, assessment of germinal center B-cell-like DLBCL (GCB) vs. non-GCB by Hans methodology [75]; MYC, BCL2, and BCL6 if previously assessed; assessment of mutational profiling if previously assessed.
- For patients with FL, assessment of t(14;18), BCL2, BCL6, and MYC if previously assessed; assessment of mutational profiling if previously assessed.
- For patients with MCL, assessment of t(11;14), Cyclin D1 expression, and BCL2 if previously assessed; assessment of mutational profiling if previously assessed.
- For patients with CLL, assessment of del (17p), del(13q), del (11q), del (6q), trisomy 12, IgVH, CD38, and Zap70 if previously assessed; assessment of mutational profiling if previously assessed (e.g., mutations that confer resistance to BTK inhibitors/ibrutinib such as Cys-481 or phospholipase C gamma 2 [PLCG2]).
- For patients with PTCL, assessment of SYK by IHC, SYK-ITK fusion, or presence of t(5;9)(q33;q22) by cytogenetics or other methodology if previously assessed; assessment of mutational profiling if previously assessed.

7.3. Dosing Cycles

7.3.1. Phase 2a Dosing Cycles

On days where pre-dose assessments are completed, patients should wait to take the study drug until they are on-site.

Patients receiving ibrutinib should continue ibrutinib for 5 days after the start of cerdulatinib, with both drugs administered at the same time. Patients should discontinue ibrutinib after the first 5 days.

7.3.2. Patient Visits After Cycle 2

All patients enrolled in the Phase 2a portion of the study are expected to be on-site for Day 1 of every cycle (e.g., C3D1, C4D1, C5D1, C6D1) except with Sponsor permission described in Section 7.3.2.1.

Certain assessments will be performed on Day 1 of every cycle throughout the duration of the study, as indicated in Appendix 1 under "All Other Cycles." These include assessment of AEs and con meds, cerdulatinib administration, and local safety labs (e.g., chemistry, hematology, urinalysis, urine or serum pregnancy as required). Study drug dispensation and accountability by site staff will also occur at these Day 1 visits, as well as the distribution and collection of completed patient diaries and other study materials.

Additional assessments will be performed every 3 cycles only, as indicated in Appendix 1 under "Additional Tests Every 3 Cycles." These include (but are not limited to) central labs and disease response assessments.

7.3.2.1. Visit Reduction for Response Patients after Cycle 12

If a patient experiences a treatment response while on study treatment, the patient may be eligible for a reduced visit schedule after Cycle 12 or at the discretion of the Sponsor. At the discretion of the Investigator based upon clinical judgement and with Medical Monitor approval, the patient's visit cycle may be reduced from every cycle (e.g., C12D1, C13D1, C14D1) to every 3 cycles (C12D1, C15D1, C18D1), corresponding with the "Additional Tests Every 3 Cycles" schedule in Appendix 1.

If a patient experiences a response and their visit reduction is approved by the Medical Monitor to every 3 cycles, the site will call the patient and conduct a telephone visit for every cycle when the patient is not on-site. During this call, site staff should obtain information about the patient's overall health, any reportable adverse events, or other relevant clinical information that would normally be collected on-site.

In these cases, patients may be dispensed enough study drug and study materials (e.g., patient diaries) to accommodate the reduced visit frequency.

7.3.2.2. 30 Days Post-Last Treatment

30 days after the last cerdulatinib dose administered, patients should return to the site for a follow-up visit consisting of a number of safety and response assessments as indicated in Appendix 1.

7.3.2.3. Unscheduled Assessments

At any time throughout the study, the following asssessments may be performed as clinically indicated:

- Unscheduled plasma PK samples may be obtained at the discretion of the Investigator upon the decision to reduce dose, interruption or discontinuation of study drug, or other (e.g., AEs that may indicate potential drug toxicity [see Section 10.1.3]). When taking unscheduled samples for PK, please note the time since the last dose and last meal in source documents.
    - In the event of a study drug interruption or dose-change, pre-dose PK samples should be collected the day study drug is restarted or a new dose is started, as well as 7 days later.
- *Cohort 6 - CTCL patients only (local laboratory)*: 1, ≥ 5 mm skin punch biopsy of a representative lesion as clinically indicated may be performed; subsequent biopsies should be from the same general site, if possible.

7.3.3. Visit Windows

Due to scheduling conflicts and the burden of study visits, patients may attend their scheduled visits within a visit window as indicated in Appendix 1.

7.3.3.1. Visit Window and Timeline Guidance

- A standard treatment cycle is defined as 28 days of treatment, and each new cycle should start 29 days from the previous Day 1 visit (e.g., C2D1 starts 29 days from C1D1).
- Each new cycle "resets" the timeline. This means that C2D15 is measured from C2D1.
- Dose interruptions that extend beyond the end of a cycle (e.g., after Day 28 of that cycle) will delay the start of the next cycle. Cycles should not be started during an interruption.
- Subjects should continue to administer study drug daily until the new cycle is started.
- For safety monitoring purposes, if a scheduled visit must be changed it is preferred that a patient comes in for a visit early instead of late.

7.4. Blood Collection

The maximum amount of blood to be drawn at a visit is ~104 mL and the total amount of blood to be drawn over a 50-week study period (including the 2-week screening period and through Week 48 of the study including a possible end-of-therapy visit) is ~548.5 mL. For a 40-kg person (the smallest participant expected to enroll in the study), this equates to maximum blood volume per body weight per visit of ~2.4 mL/kg and a total blood volume per body weight per average 6-week period of ~1.6 mL/kg. These quantities of blood are within accepted limits of 3.0 mL/kg of body weight for a single blood draw and 7.0 mL/kg of body weight for a 6-week period [76].

7.5. Concomitant Medications and Other Guidance

All concomitant medications used during the study and within 14 days prior to Screening must be reported on the appropriate CRF.

7.5.1. Prohibited Medications/Procedures

- Chemotherapy, radiation therapy, hormonal therapy or any investigational anti-neoplastic agent for the active treatment of cancer are prohibited. Patients may continue on adjuvant hormonal therapy for prostate or breast cancer, as long as there is no detectable disease at study entry.
- Systemic steroids, at doses greater than the equivalent of 20 mg prednisone daily, with the exception of intermittent use for the treatment of emesis, are prohibited. Steroid inhalers for medical conditions are permitted. Patients needing pulse corticosteroids for other medical conditions should be discussed with the Sponsor's Medical Monitor.

- Nasal flu vaccine is prohibited because the nasal vaccine is a live, attenuated virus; however, flu injections, which are nonviable antigens, are permitted (see Section 7.5.2).

7.5.2. Permitted or Mandated Medications

- Anti-emetic agents for the treatment of nausea and vomiting are permitted.
  - No constraint will be placed on the use of growth factors during subsequent treatment; however, prophylactic use is discouraged and adherence to American Society of Clinical Oncology (ASCO) guidelines is recommended.

7.5.2.1. Antimicrobial Prophylaxis

- *Pneumocystis* prophylaxis is required in all patients receiving cerdulatinib, and study patients should be monitored closely with frequent cell counts for evidence of infection or bone marrow suppression. Bactrim™ (sulfamethoxozole/trimethoprim) 1 DS tab/day is the recommended prophylaxis regimen and will cover both *Pneumocystis jirovecii* and *Nocardia*. Other recommendations may be found in the National Comprehensive Cancer Network (NCCN) guidelines [77]. For patients unable to take Bactrim, atovaquone, or pentamadine (inhaled or IV) may be considered. Dapsone is not recommended because of the potential for drug interactions and methemoglobinemia.
- Patients should also receive prophylaxis for herpes simplex virus infection per NCCN guidelines [77].
- Immunizations or vaccinations (for such things as influenza or pneumonia) are encouraged prior to study entry. Note that nasal flu vaccines should not be administered to patients because the nasal vaccine is a live, attenuated vaccine, whereas flu shots are nonviable antigens (see Section 7.5.1).
- Prophylaxis for tumor lysis syndrome is permitted at the discretion of the treating physician, based on clinical characteristics.

7.5.3. Cerdulatinib and CYP3A4

Cerdulatinib is a substrate for CYP3A4 and may also decrease expression levels of CYP3A4 enzyme activity in patients, thus potentially augmenting the AE profile of other drugs. To avoid possible drug-drug interactions, strong inhibitors, CYP3A sensitive substrates, and inducers of CYP3A4 should be avoided in patients receiving cerdulatinib. An inhibitor of CYP3A4 would reduce the metabolism of cerdulatinib and could result in high concentrations that could cause AEs. An inducer of CYP3A4 could result in lower than desired levels of cerdulatinib and lessen the likelihood of efficacy. Additionally, cerdulatinib can cause other medications to accumulate to levels that result in toxicity due to lower levels of CYP3A4 being expressed. Because of this effect CYP3A sensitive substrates need to be considered. If the Investigator feels that use of a strong inhibitor or strong inducer of CYP3A4 is necessary, this should be discussed with the Sponsor's Medical Monitor. Appendix 3 provides a list of such CYP3A4 substrates and strong

inhibitors/inducers. Physicians should monitor for potential drug-drug interactions, and a dose adjustment (lowering) for CYP3A sensitive substrates should be considered on a case-by-case basis by the treating physician.

7.6. Study Committee

Select study participants will comprise the Study Committee (e.g., the selected Principal Investigators, Portola's Medical Monitor, Clinical Study Manager, and/or Drug Safety Medical Monitor). Other Portola or outside personnel may be called or consulted as needed.

- Phase 1: Upon the completion of the initial 28-day treatment period (Cycle 1) for all patients in any cohort, the Study Committee will convene via teleconference or in person to review all available DLT, AE, and any other clinical or laboratory data for the patients in that cohort. The Study Committee will determine whether it is safe to escalate to the next dose level of cerdulatinib or whether the MTD or MAD has been reached. If it is safe to continue, the Study Committee will determine the next dose level to be studied.
- Phase 2a: The Study Committee will meet periodically to review available safety and efficacy data from the study. Following the first meeting of the Study Committee, subsequent meetings will be held periodically as needed. Members of the Portola study team, such as representatives from Biostatistics, Drug Safety, Clinical Development, and Clinical Operations may participate in the meetings as needed. Data to be evaluated may include (but are not limited to): deaths, other SAEs; AEs, including treatment-related AEs; reasons for treatment discontinuation or dose modification/ interruption, trends in laboratory evaluations, and efficacy.
- For the combination cohort with rituximab, the Study Committee will evaluate (using the assessments as outline above) the first 3 to 6 patients who have completed Cycle 1 before allowing further enrollment in the cohort. Afterwards, the cohort can be evaluated with the rest of the other cohorts as above.

8.0 ASSESSMENT OF EFFICACY

8.1. Response Criteria

Response in NHL patients will be evaluated using The Lugano Classification [4]; in CLL patients using the Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia [2]; in leukemic forms of PTCL (ATLL, PLL, LGL) using disease appropriate response criteria [77]; and in CTCL patients using the modified Severity Weighted Assessment Tool (mSWAT) and other measures as appropriate [5]. Appendix 4 provides definitions and detailed descriptions of response criteria as well as guidance on selection of lesions for evaluation. Redacted copies of radiology reports will be sent to the Sponsor for review.

8.2. Exploratory Efficacy

8.2.1. Global Health Questionnaire

Patients will be asked to complete a Global Health Questionnaire (Appendix 8) to assess whether patients feel their overall health is improving on this study. The correlation between markers of inflammation with clinical response and the Global Health Assessment will be evaluated.

9.0 PHARMACOLOGY ASSESSMENTS

9.1. Pharmacokinetic Assays

Plasma samples will be obtained at selected time points (detailed in Appendix 1) and analyzed for the concentration of cerdulatinib and possible metabolite identification. Sample assay for drug concentrations will be performed using a validated LCMS method. Details on the collection, processing, storage, and shipment of samples are contained in the Study Laboratory Manual.

9.1.1. Phase 1 Pharmacokinetic Analysis

The following PK parameters of cerdulatinib will be calculated for all patients:

- Plasma half-life ($t_{½}$), determined by linear regression of the log concentration on the terminal portion of the plasma concentration-time curve. Terminal half-life is calculated as ln(2)/(-β), where β is the slope of the terminal portion of the log concentration-time curve.
- Time to maximum observed plasma concentration (T_{max}).
- Maximum observed plasma concentration (C_{max}).
- Minimum observed plasma concentration (C_{min}).
- Area under the plasma concentration-time curve from 0 to last measurable concentration ($AUC_{0\text{-}last}$) computed using the linear trapezoidal rule.
- Total area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$), computed as:

$$AUC_{0\text{-}\infty} = AUC_{0\text{-}last} + C_{plast} /(- \beta)$$

  where $AUC_{0\text{-}last}$ is the area under the curve from time 0 to the time point of the last measurable concentration above the quantitation limit; C_{plast} is the last measurable concentration above the quantitation limit; and β is defined as above.
- Clearance of cerdulatinib (CL/F).
- Volume of distribution of cerdulatinib at steady state (V_{ss}/F).
- Amount of drug excreted in urine over the sampling interval (Ae) for those patients for whom total volume of urine was collected.
- Accumulation ratio, calculated by $AUC_{0\text{-}12}$ at steady-state/$AUC_{0\text{-}12}$ following the first dose for those patients for whom the 12 hour sample was collected.

9.1.2. Phase 2a Pharmacokinetic Analysis

In order to further characterize the PK of cerdulatinib (specifically, C_{min}), plasma samples during the Phase 2a portion of the study will be taken pre- and post-dose at various visits during the study as described in Appendix 1.

The date and time of last cerdulatinib dose prior to any PK assessment should be recorded.

Unscheduled plasma samples may also be collected at the discretion of the Investigator (e.g., in the event of an AE) as described in Section 7.3.2.3.

9.2. Pharmacodynamic Assays

Serum will be obtained at various time points throughout the trial (detailed in Appendix 1) to determine the effects of cerdulatinib on markers of inflammation. DNA and RNA will be isolated from optional tumor biopsy specimensto assess genetic mutations relevant to the disease and the mechanism of action of cerdulatinib (see Appendix 1 and the Study Laboratory Manual).

- Quantification of serum proteins.
- Quantitative PCR for tumor relevant transcripts.
- Hybridization of RNA to gene arrays.
- DNA sequencing to identify disease-relevant mutations.

10.0 ASSESSMENT OF SAFETY

Safety and tolerability will be monitored and determined by serial physical exams, vital signs, hematology and chemistry laboratory studies, and reported AEs (including deaths and other serious adverse events [SAEs] and treatment-emergent AEs).

10.1. Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and pregnancies; performing protocol-specified safety laboratory assessments; measuring protocol-specified vital signs; and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Syneos Safety Department, as outlined in Section 10.2.1.

10.1.1. Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which may or may not have a causal relationship with the treatment. An AE can be any of the following:

- Unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug-related
- Any newly occurring event or exacerbation of previous condition (e.g., increase in severity or frequency) since the administration of study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

10.1.2. Serious Adverse Event (SAE)

An SAE is any AE, occurring at any dose of any study medication, regardless of causality that:

- Is fatal (i.e., the adverse event actually causes or leads to death).
- Is life-threatening (i.e., in the opinion of the Investigator or Study Sponsor, the patient was at immediate risk of death from the reaction as it occurred).
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother who was exposed to study drug or where the father was exposed to study drug before conception. Is an important medical event in the investigator's judgment (i.e., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe," since these terms are NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (according to NCI CTCAE criteria per section 10.2.2); the event itself, however, may be of relatively minor medical significance. This is NOT the same as "serious," which is based on the strict regulatory definitions listed above and serves as a guide for defining regulatory reporting obligations. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted serious criteria. Thus, severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

10.1.3. Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs are serious AEs that are both unexpected (i.e., the nature or severity is not expected from the information provided in the IB) and assessed by the Investigator or Portola Medical Monitor to have a reasonable possibility of a causal relationship to the investigational medical product(s). SUSARs require reporting to the Competent Authorities, and Ethics Committees within an expedited timeline (7 calendar days for fatal / life-threatening SUSARs, 15 calendar days for all other SUSARs). Thus it is required that the Investigator complete the SAE form and report all SAEs within 24 hours of his/her awareness of the event to the Syneos Safety Department. Additionally, Syneos Safety Department, on behalf of Portola, will immediately notify the Investigator if any additional safety or toxicology information that impacts patient safety becomes available during the study. All SUSARs will be provided to all Investigators for submission to their respective IRBs per local requirements and when information that impacts patient safety becomes available during the study. It is the responsibility of the Investigator to promptly notify the IRB/Independent Ethics Committee (IEC) of all SUSARs involving risk to human patients.

10.2. Methods and Timing for Capturing and Assessing Safety Parameters

The investigator is responsible for ensuring that all AEs (Section 10.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (Section 10.1.2), severity (Section 10.2.2), and causality (Section 10.2.3).

10.2.1. Adverse Event Reporting Period

To comply with regulatory requirements, all SAEs, regardless of causality, that occur from the date of signing of informed consent until 30 days after the last study drug treatment (or initiation of the next therapeutic regimen prior to the 30 days), must be reported to Syneos Safety Department within 24 hours from Investigator awareness of the SAE.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported to Syneos Safety Department. These pre-dose adverse events will be collected on the AE eCRF and assessed as not related to study drug, but will be assessed for relationship to study procedures/tests and interventions.

After initiation of study drug, all treatment emergent adverse events (TEAE), regardless of relationship to study drug, will be reported until **30 days after the last dose of study drug**. Any SAE that occurs with an onset date later than 30 days after completion of the study and that the Investigator considers to be related to study medication must be reported to the Syneos Safety Department.

To report any SAEs, the SAE Report Form provided to the clinical study site must be completed with the available information. The information collected must include at minimum the following: patient number, study drug(s) received, the event term, the serious criteria met for the AE, a narrative description of the event, and an assessment by the Investigator of the severity/intensity of the event and relationship to study drug(s). The SAE report should be sent to Syneos Safety Department by email (see contact information below). Follow-up information on the SAE should be sent promptly by the Investigator to Syneos Safety Department when any additional relevant information about the SAE becomes known to the Investigator, or as requested by Syneos Safety Department.

SAE Reporting Contact Information

Syneos Safety Department

[redacted]

Please refer to the SAE reporting form for more information.

All AEs and SAEs should be monitored until they are resolved or the patient dies. Additionally, the Investigator must determine both the severity of the event and the relationship of the event to study drug.

10.2.2. Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event, per the definition of serious adverse event in Section 10.1.2.

[d] Grade 4 and 5 events must be reported as serious adverse events, per the definition of serious adverse event in Section 10.1.2.

10.2.3. Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

The following categories should be used in the causality assessment of adverse events:

Related

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; and
- Cannot be explained by other factors, such as the subject's clinical state, therapeutic intervention, or concomitant therapy.
- The response to withdrawal of the drug (dechallenge) should be clinically plausible and the event reoccurs on rechallenge if patient is re-exposed.

Probably Related

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; and
- Was unlikely to have been produced by other factors, such as the subject's clinical state, therapeutic intervention, or concomitant therapy.

Possibly Related

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; but
- Could have been produced by other factors, such as the subject's clinical state, therapeutic intervention, or concomitant therapy.

Unlikely

The AE:

- Does not follow a reasonable temporal sequence from the time of study drug administration; and
- Was most likely produced by other factors, such as the subject's clinical state, therapeutic intervention, or concomitant therapy.

Unrelated

This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (e.g., the patient's clinical state, therapeutic intervention or concomitant therapy) and do not meet the criteria for study drug relationship listed under Probable, Possible, or Unlikely.

An AE with causal relationship not initially determined will require follow-up to assign causality.

10.2.4. Procedures for Recording AEs

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one AE term should be recorded in the event field on the Adverse Event eCRF.

All AEs spontaneously reported by the patient and/or in response to an open-ended question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate forms in the eCRF.

Only one AE term should be recorded in the event field on the Adverse Event eCRF. When possible, a unifying diagnosis, or signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For example, the combination of general malaise, mild fever, headache and rhinitis should be described as a "common cold" rather than listing each symptom separately.

10.2.4.1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases; record Tumor Lysis Syndrome rather than hypocalcemia, hyperkalemia, hyperuricemia, etc.). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

10.2.4.2. Adverse Events that are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

10.2.4.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF with the severity (intensity or grade) of the events recorded at the time the event is first reported.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs, or notes a change in severity or seriousness. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF. For example:

- If Grade 1 vomiting has worsened to Grade 2 five days after onset, the Grade 1 vomiting is resolved on the date when this severity changed, and Grade 2 vomiting is recorded as a new event on the eCRF with onset date reflecting the change in severity.
- If non-serious event of neutropenia required hospitalization five days after onset, the event is resolved on the hospitalization date, and a new SAE of neutropenia is recorded on the eCRF with start date reflecting when the event required hospitalization.

10.2.4.4. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's in the investigator's judgment
    - Note: For oncology trials, certain abnormal values may not qualify as AEs.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

10.2.4.5. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (Section 10.2.4.3 provides details on recording persistent AEs).

10.2.4.6. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

10.2.4.7. Deaths

Death should be considered an outcome and not a distinct event. All deaths (including deaths due to progression of the underlying malignancy) that occur during the protocol-defined adverse event period should be reported as SAEs, regardless of attribution to study drug. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept (e.g., respiratory failure) with a fatal outcome. When the event that led to death cannot be identified (e.g., sudden death of unknown origin) report "sudden death" as the adverse event and update it when new information clarifies the event that led to death. Only one AE can be reported with a fatal outcome for each patient who dies. Other AEs that continued up to time of death should be reported with an outcome of not recovered/resolved. In the event that the death is attributed solely to progression of the underlying malignancy, the AE term should be reported as "Disease Progression."

10.2.4.8. Lack of Efficacy or Worsening of Underlying Malignancy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs (except deaths; see Section 10.2.4.7). Example: a patient with disease progression documented by metastatis/new tumors in the liver also has concurrent increases in transaminases. Every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether a change in the patients condition, is due to disease progression, it should be reported as an AE. Example: a patient with disease progression documented by metastatis/new tumors in the liver also has concurrent new onset kidney failure (scan does not reveal kidney metastasis).

10.2.4.9. Preexisting Medical Conditions

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.2.4.10. Hospitalization or Prolonged Hospitalization

The following hospitalizations are not considered SAEs in this clinical trial:

- Admissions per protocol for a planned medical/surgical procedure. Planned hospital admissions or planned surgical procedures for an illness or disease that existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs, unless they occur at a time other than the planned date for a reason such as a worsening of the underlying disease/illness/symptoms.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

10.2.4.11. Adverse Events Associated with an Overdose or Error in Drug Administration

Overdose is defined as any dose in excess of the assigned dose of cerdulatinib greater than or equal to 90 mg total dose in one day or greater than 375 mg/m^2 of rituximab per day.

All overdoses meeting the above criteria must be recorded as an AE (Verbatim term = accidental overdose) on the eCRF. All overdoses must be reported to the Syneos Safety Department within 24 hours of awareness including information for dose received vs. dose assigned, and treatment

given to the patient whether or not there are any signs or symptoms. Any signs or symptoms resulting from an overdose must also be recorded as an AE on the eCRF and reported on the SAE form (medically important event) as separate adverse event(s) (see Section 10.2).

Any dose that exceeds the assigned dose of cerdulatinib but is less than the 90 mg total dose in one day threshold for Overdose should be reported to the Sponsor Medical Monitor and captured appropriately in the Cerdulatinib Administration eCRF.

All other significant dosing or medication errors that may not meet AE criteria (e.g., inadvertent dosing of non-study subject) should be reported to the Syneos Safety Department within 24 hours of awareness.

10.2.4.12. Adverse Events in Individuals Not Enrolled in the Study

If an AE inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to Syneos SafetyDepartment, by scanning and emailing the form using the email address provided to investigators.

10.2.4.13. Pregnancy Exposure and Birth Events

If a female study patient becomes pregnant during study drug administration or within 16 weeks after date of last dose, the Investigator should be informed immediately and study treatment must be discontinued if not already terminated. The Investigator must urgently email a completed Pregnancy Form to Syneos Safety Department (Section 10.2).

If a female partner of a male study patient is pregnant or suspects she is pregnant by the male study patient (between study drug administration and up to 16 weeks after the termination visit), the Investigator should be informed immediately. The Investigator must advise the male patient to have his female partner inform her treating physician immediately, and the Investigator must urgently email a completed Pregnancy Report Form to Syneos Safety Department.

In all cases, the pregnancy must be followed up through delivery or other fetal outcome. Newborns should be monitored until at least 8 weeks of age for any potential congenital anomalies. The Investigator should promptly report any abnormal fetal outcome (i.e., congenital anomaly or birth defect, spontaneous or therapeutic abortion, stillbirth, pre-mature birth or outcome other than live normal birth) on an SAE form.

11.0 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

11.1. General Considerations

It is anticipated that all statistical summaries will be performed using SAS software Version 9.3 (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used for the production of graphics.

11.1.1. Analysis Populations

The safety analysis population will consist of all patients treated with at least 1 dose of study medication (cerdulatinib). Safety data will be summarized by dose level, based on the original assigned dose of study drug.

The efficacy analysis population for the primary and secondary efficacy endpoints will consist of all patients who have taken at least 1 dose of study medication and have had at least 1 post-baseline tumor assessment. Efficacy will be summarized separately for Phase 1 and 2a, and within Phase 2a, efficacy will be summarized by cohort and dose level.

The PK and PD analysis populations will consist of all patients who have received the requisite treatments and have data at the required time points. Any windows for timing of measurements, etc., will be specified in the SAP.

11.1.2. Cohort Comparability

Baseline and demographic characteristics will be summarized for Phase 2a by dose cohort and overall. No formal statistical analyses of these data are planned, but descriptive statistics may be used to aid in interpreting results.

11.1.3. Efficacy Endpoints and Analyses

Responses will be summarized with patients classified as CR, PR, SD, PD, or not evaluable. The overall response rate (CR+PR) and clinical benefit rate (CR+PR+SD) will be summarized along with 2-sided exact 95% confidence intervals. Responses will be based on CT or CT/PET, evaluated per IWG Criteria [3] for patients with lymphoma and on peripheral lymphocyte counts and bone marrow biopsy results for patients with CLL [2]. Listings of tumor response for each patient will also be provided. Responses will be summarized separately for each dose level in Phase 1 and for each cohort and dose level in Phase 2a. Due to differences in underlying disease and prior treatment, response rates considered clinically significant and that would prompt further study will depend on the cohort. Such summaries will also depend on the safety and tolerability profile observed. While it is anticipated that a 30 to 40% response rate in a future study will be sufficient to support further investigation, no criteria for success in this study are specified.

In addition to the tumor response rates described above, the following efficacy endpoints will be assessed (defined in Table 3 and reproduced below):

- DOR (duration of response) – defined as the time from the first documentation of PR or CR to the earlier of the first documentation of disease progression or death from any cause.
- PFS (progression-free survival) – defined as the time from the start of cerdulatinib treatment to the earlier of the first documentation of disease progression or death from any cause.
- LNR (lymph node response) – defined as the proportion of patients who achieve a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes.
- TTR (time-to-treatment response) – defined as the time from the start of cerdulatinib treatment to the first documentation of CR or PR.

11.1.4. Pharmacokinetic Analyses, Phase 1 and 2a

Pharmacokinetic (PK) parameters (described in Section 9.1.1 and Section 9.1.2) will be calculated for each patient and summarized for patients with sufficient samples available. During Phase 2a, plasma samples will be taken as described in Appendix 1.

11.1.5. Pharmacodynamic Analyses, Phase 1 and 2a

A number of PD parameters will be measured serially as described in Section 9.2. At each time point, each of these parameters will be summarized by dose level. In addition, the parameters over time will be plotted for each patient and dose cohort. No formal statistical analyses are planned.

11.1.6. Safety Analyses, Phase 1 and 2a

The primary safety endpoint is the incidence of Grade 3 or higher clinically significant toxicity by dose level, and the secondary safety endpoints are as follows:

- Adverse event profile (classified by NCI-CTCAE v5.0).
- Clinically significant changes in vital signs, physical exams by dose level.
- Changes in hematology and chemistry laboratory parameters by dose level.

The incidence of Grade 3 or higher clinically significant toxicity will be summarized and listed by dose cohort for Phase 1.

Adverse events (AEs) will be graded according to the NCI-CTCAE v4.0 (Phase 1) and NCI_CTCAE v5.0 (Phase 2a) and coded according to the latest MedDRA version available at the time of database creation. The number and percent of patients with any AE will be presented by System Organ Class (SOC) and preferred term for each cohort will be summarized by dose

cohort for Phase 1 and by Cohort for Phase 2a. An additional summary will include all patients who received the dose used in Phase 2a.

Vital signs, laboratory parameters, and ECG intervals will be summarized and listed by time point for each dose cohort for Phase 1 and by Cohort for Phase 2a. No formal statistical analyses are planned.

11.2. Sample Size Considerations

11.2.1. Phase 1 Sample Size

The sample size is based on clinical judgment and is typical of studies of this type. 43 patients were dosed with cerdulatinib. The Phase 1 portion of the study is closed to enrollment.

11.2.2. Phase 2a Sample Size

Each of the 6 cohorts will consist of approximately 20 to 50 patients with relapsed or refractory disease. Initial enrollment into any cohort will be up to 20 patients; cohorts may be expanded to 40 to 50 evaluable patients. A total of approximately 240 patients are planned. If fewer than 2 responses are seen in the first 20 patients, enrollment in the cohort will be closed, as the upper bound (UB) of the 95% confidence interval would be approximately 25%. If 2 or more responses are seen, the cohort may be expanded.

Patients in Cohorts 1, 3, 4, 5, and 6 will receive single-agent cerdulatinib. Patients in the Cohort 2 will receive cerdulatinib in combination with rituximab. The composition of each cohort is described in Table 6.

11.3. Missing Data

No imputation of missing data will be performed. Patients who do not have sufficient information for evaluation of response will be listed with the reason for missing response, and the count will be summarized.

11.4. Multiplicity

With multiple doses investigated in Phase 1 and multiple cohorts investigated in Phase 2a, there is an inflated chance of making an incorrect conclusion from this study. No adjustments will be made to the efficacy summaries in Phase 1 or to the safety summaries in Phase 2a to account for multiplicity. If 6 cohorts are assessed in Phase 2a, the difference between the observed rate and the underlying population rate will be biased if only the cohort with the observed rate most above an expected rate is considered. This will be informally considered when evaluating the data.

11.5. Data Safety Monitoring

There will be no formal DSMB for this trial. The composition of the Study Committee and its functions are specified in Section 7.6.

12.0 INVESTIGATOR AND SPONSOR OBLIGATIONS

12.1. Documentation Required for Study Initiation

Before initiation of the study, the Investigator must provide the following documentation required by FDA regulations, including but not limited to, (copies of which must be maintained by the Investigator):

1. FDA Form 1572.
2. Curriculum vitae of the Investigator.
3. A signed copy of the IRB or Ethics Committee approval notice for protocol and informed consent.
4. A copy of the IRB or Ethics Committee approved informed consent.
5. Completed financial disclosure form for the Investigator.

12.2. Data Reporting and Case Report Forms (CRF)

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to help text for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor. Data entered into an eCRF will be processed in a US 21 CFR Part 11-compliant system.

All eCRFs should be completed by designated, trained site staff. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the subject's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient's clinical status.

The Investigator or designated representative should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. eCRFs should be reviewed and electronically verified, signed, and dated by the Investigator or designee.

12.3. Deviation from the Protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, then notify the Sponsor's MM, the Safety Monitor, and the IRB immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate CRF. The Sponsor will not assume any responsibility or liability for any deviation or change from the protocol.

12.4. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Portola will visit the investigational study site to perform the following:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Portola or its representatives. This will be documented in a Clinical Study Agreement between Portola and the Investigator.

During the study, a monitor from Portola or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Portola.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Portola and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

12.5. Audits and Inspections

Authorized representatives of Portola, a regulatory agency, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Portola audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, International Council for Harmonisation (ICH) Guideline for Good Clinical Practice, and any applicable regulatory requirements. The Investigator should contact Portola immediately if contacted by a regulatory agency about an inspection.

12.6. Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

12.7. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates study drug was received from Portola and dispensed to the patients. All drug supplies must be accounted for during the study and at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies will be destroyed at the site in accordance with site standard operating procedures approved by Portola or returned to Portola (or designated depot) after written authorization is obtained. The Investigator will maintain a record of the amount, reason and dates when unused supplies were either destroyed or returned to Portola. All records will be retained as noted in Section 15.2.

12.8. Disclosure of Data

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the FDA and the study Sponsor, Portola, and its agents and representatives will need to review patient medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the patient's identity will remain confidential.

13.0 QUALITY CONTROL AND ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Portola may conduct a quality assurance audit. Please see Section 12.5 for more details regarding the audit process.

14.0 ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Portola before he or she can enroll any patient/patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Portola will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH Guideline for Good Clinical Practice, applicable regulatory requirements and the Portola's policy on Bioethics.

14.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

15.0 DATA HANDLING AND RECORD RETENTION

15.1. Inspection of Records

Portola will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Portola or the regulatory agency to review any documentation relating to the study, the Investigator must permit access to such records.

16.0 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

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18.0 APPENDICES

The following appendices are provided:

Appendix 1: Schedule of Assessments – Phase 2a (Exploratory)

Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Appendix 3: Strong CYP3A4 Inhibitors and Inducers and CYP3a Sensitive Substrates

Appendix 4: Response Definitions for B-cell NHL and PTCL, CLL, and CTCL

Appendix 5: Prognostic Factors

Appendix 6: Differential of ABC vs. GCG type of DLBCL by IHC-Hans Methodology

Appendix 7: Staging Systems for CLL and NHL

Appendix 8: Global Health Assessment

Appendix 9: Cockcroft-Gault Method for Evaluating Creatinine Clearance

Appendix 10: Likert Scale

Appendix 11: T-cell Lymphoma Classifications

APPENDIX 1. SCHEDULE OF ASSESSMENTS – PHASE 2A (EXPLORATORY)

PROCEDURES	Pre-Treatment	Phase 2A Treatment Period																		Follow-up
	SCREENING	CYCLE 1										CYCLE 2				CYCLE 3 (and C6, C9, C12, C15, C18+)		CYCLES 4 & 5 (and C7, C8, C10, C11, C13, C14+)		30 Days Post-last Treatment
		D1		D2	D8		D9	D15		D22 Cohort 2 Only		D1		D15		D1		D1		
	D -21	Pre-dose	Post-dose	Pre-dose	Pre-dose	Post-dose	Pre-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	
Visit Windows (Days)	Within 21 Days Prior to C1D1	N/A		N/A	±1		N/A	±2		±2		±3		±2		±3		±3		±3
General/Safety Assessments																				
Obtain Informed Consent	X																			
Review Inclusion/Exclusion Criteria	X	X																		
Medical History and Prognostic Factors [1]	X	X																		
Physical Examination	X	X			X			X				X				X				X
Height	X																			
Weight	X	X										X				X		X		X
Vital Signs [2]	X	X	X		X	X		X	X	X	X	X		X		X		X		X
12-Lead ECG	X																			X
ECOG Performance Status	X	X										X				X				X
Global Health Assessment [3]	X	X			X			X				X				X				
Concomitant Medications	X [4]	X [4]			X			X		X		X		X		X		X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cerdulatinib Administration [5]		X		X	X		X	X		X		X		X		X		X		
Rituximab Administration (Cohort 2 Only) [6]			X			X			X		X						X [7]		X [7]	
Local Disease Assessments and Laboratory Tests																				
Bone Marrow Biopsy and Aspirate [8]	X															X		X		
CT or CT/PET [9]	X															X				
Optional Lymph/Tumor Node Biopsy [10]		At any time throughout the study																		
Optional Tumor Block/Unstained Slides [10]	X																			
EBV PCR [11]	X																			
HIV/HBV/HCV infection testing [12]	X																			
Serum Chemistry and Hematology [13]	X	X			X			X				X		X		X		X		X
Urinalysis (microscopic analysis as clinically indicated)	X	X										X				X		X		X
Urine or Serum Pregnancy [14]	X	X										X				X		X		X
PT/PTT/INR	X																			X
Beta-2 Microglobulin, Lymphocyte Subsets, Immunoglobulin Levels [15]	X [16]	X			X			X				X				X				
CRP and ESR-Westergren (Sed. Rate)		X			X			X				X				X				
Prognostic factors: cytogenetics (FISH), IgVH, Zap70, CD38 (Cohort 4 - CLL/SLL Only) [17]		X																		

PROCEDURES	Pre-Treatment	Phase 2A Treatment Period																		Follow-up
	SCREENING	CYCLE 1										CYCLE 2				CYCLE 3 (and C6, C9, C12, C15, C18+)		CYCLES 4 & 5 (and C7, C8, C10, C11, C13, C14+)		30 Days Post-last Treatment
		D1		D2	D8		D9	D15		D22 Cohort 2 Only		D1		D15		D1		D1		
	D -21	Pre-dose	Post-dose	Pre-dose	Pre-dose	Post-dose	Pre-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	
Visit Windows (Days)	Within 21 Days Prior to C1D1	N/A		N/A	±1		N/A	±2		±2		±3		±2		±3		±3		±3
CTCL Disease Assessment – mSWAT and Likert Scale (Cohort 6 - CTCL Only)	X											X				X		X		
CTCL Disease Assessment – Flow Cytometry for Sézary Cells and Photographs of Skin Involvement (Cohort 6 - CTCL Only)	X															X				
Response assessment for leukemic subtypes	X															X				
Skin Punch Biopsy (Cohort 6 - CTCL Only) [18]	X											X								
Central Laboratory Tests																				
Plasma PK [19]		X	X [19]	X [19]	X	X [19]	X [19]	X				X		X		X				
Serum Cytokine Biomarker Analysis		X			X							X				X				

CLL = Chronic lymphocytic lymphoma; CT = Computed tomography; EBV = Epstein-Barr virus; ECG = Electrocardiogram; ECOG = Eastern cooperative oncology group; FISH = Florescence in situ hybridization; iNHL = indolent non-Hodgkin lymphoma; lab = Laboratory; PCR = polymerase chain reaction; PET = Positive-emission tomography; PK = Pharmacokinetic; PT/PTT/INR = Prothrombin time, partial thromboplastin time/international normalized ratio; SOC = Standard of care

1. Medical history should include a redacted copy of the pathology report and any supporting pathology information, including the original pathology report from the diagnosis (which may include additional mutational analysis by sequencing, FISH, IHC, cytogenetics, etc.,) to be available for Sponsor review.
2. Vital signs include temperature, respiration, blood pressure and heart rate, and should be obtained after at least 5 minutes in the sitting or semi-recumbent position. Post-dose vital signs should be obtained at 1.0 hour post-cerdulatinib administration for all patients except those in Cohort 2 for all onsite visits. For patients in Cohort 2 (cerdulatinib + rituximab), on visits when rituximab is administered, post-dose vital signs should be obtained at 0.5, 1.0, 2.0, 3.0, and 4.0 hours post-cerdulatinib dosing (or per standard of care), and then as clinically indicated. The collection window for vital signs is ± 10 minutes.
3. Administer Global Health Assessment before any other protocol procedures are performed and before any protocol-related information is communicated.
4. Record all medications including over the counter preparations, herbals, and vitamins taken in the 14 days prior to Cycle 1 Day 1.
5. Dosing begins on Day 1 and continues daily until treatment interruption or study discontinuation.
6. Rituximab dose is 375 mg/m^2. Rituximab infusion should start immediately after cerdulatinib is taken.
7. After Cycle 1, rituximab should be administered on Day 1 only of Cycles 4, 6, 8, and 10.
8. For CLL patients only, a bone marrow biopsy and aspiration will be completed before Day 1 (within 6 weeks/42 days prior to Day 1) through the local lab and be repeated as clinically indicated. For all other patients with a history of bone marrow involvement prior to entering the study, a repeat biopsy should be performed to confirm a complete response or as clinically indicated.
9. CT or CT/PET of chest, abdomen, pelvis, and any other areas of lymphoma may be obtained within 28 days prior to Cycle 1 Day 1; redacted copy of the report(s) to be available to the Sponsor for review. Subsequent CT or CT/PET assessments may be performed within 7 days prior to the scheduled visit and as clinically indicated. For CTCL patients, if baseline scan is negative for nodal/visceral/other disease, a repeat CT or CT/PET is not necessary except to confirm CR and may be done as clinically indicated. In the event of a Complete Response, confirmatory scans should be obtained no less than 4 weeks following determination of response. Copies of scans should be made available to Sponsor upon request. Additionally, obtain copy of molecular/mutation profile if obtained as standard of care.
10. Optional: An archival tissue block or unstained slides may be submitted during Screening after eligibility has been confirmed. Tumor biopsies may also be obtained at the discretion of the treating physician as clinically indicated. For all tumor biopsies and samples, submit a formalin-fixed paraffin embedded tissue (FFPE) block or a minimum of 10 (preferably 20) unstained, freshly cut FFPE tissue slides from lymph node or other biopsies. Additional information available in the Lab Manual.
11. Obtain EBV PCR at screening. If EBV PCR was not obtained at screening, it should be obtained at the next visit. In addition, post-baseline EBV PCR should be obtained for any patient with an unexplained fever if there is clinical suspicion of EBV reactivation.
12. Testing for HIV, HBV, and HCV will be performed if the patient does not have documentation of a negative hepatitis panel and negative HIV history within the 12-week period prior to enrollment.
13. Serum chemistry includes: sodium, potassium, chloride, magnesium, CO_2 (HCO_3), glucose, blood urea nitrogen (BUN), creatinine, AST (SGOT), ALT (SGPT), lactate dehydrogenase, total protein, albumin, alkaline phosphatase, calcium, phosphorous, bilirubin, uric acid, amylase, and lipase. Hematology includes: hemoglobin, hematocrit, WBC, platelet count, complete blood count (CBC) with differential. Grade 3 or greater increases in ALT or AST require liver function testing to be repeated within 72 hours of initial test.
14. Results of urine or serum pregnancy testing must be available prior to study drug administration.
15. Quantitative immunoglobulins: quantitative levels of IgA, IgE, IgG, and IgM Lymphocyte subsets: quantitation of absolute numbers (or %) of CD3+, CD4+, CD8+, CD16/56+, and CD19+ by flow cytometry.
16. Results obtained within 60 days prior to C1D1 may be used in lieu of the Screening assessment.
17. For IgVH, results obtained within 3 months prior to C1D1 may be used.
18. Skin punch biopsy is mandatory for all patients with CTCL and should be a ≥ 5 mm punch biopsy of a representative lesion. A biopsy should be obtained from 2 different areas of disease if possible (e.g., plaque and nodular lesions). Subsequent biopsies should be from the same general site if possible. At least 10 unstained slides or a FFPE tissue block should be submitted.
19. Serial PK samples will be collected on C1D1 and C1D8 at pre-dose (i.e., within 60 minutes prior to the dose), and 1, 2, 4, 6, 8, and 24 hours post-dose (collection window is ± 10 minutes, except for the 24-hour post-dose timepoint [± 30 minutes]). The 24 hours post-dose PK samples collected on C1D2 and C1D9 should be collected prior to dosing in-clinic that day. If a patient is not dosed at a particular visit but is due to be dosed, a trough PK assessment should still be performed. In addition to times specified in this row, obtain a PK sample whenever a patient experiences a dose reduction/interruption, study drug discontinuation, and any AE that may indicate potential drug toxicity. Section 7.3.2.3 provides additional information.

APPENDIX 2. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Status

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

APPENDIX 3. STRONG CYP3A4 INHIBITORS AND INDUCERS AND CYP3A SENSITIVE SUSBSTRATES

To avoid possible drug-drug interactions, strong inhibitors and inducers of CYP3A4 and CYP3A sensitive substrates should be avoided in patients receiving cerdulatinib (Table A3-9 and Table A3-10). If the Investigator feels that use of these medications is necessary, this should be discussed with the Medical Monitor. A dose adjustment (lowering) for CYP3A sensitive substrates may be considered on a case-by-case basis.

Table A3-9: Strong CYP3A4 Inhibitors and Inducers

Strong Inhibitors	Strong Inducers
Clarithromycin	Barbiturates
Telithromycin	Efavirenz
Ketoconazole and Posaconazole	Nevaripine
Itraconazole	Pioglitazone
Fluvoxamine	Rifampin
Nefazodone	Rifabutin
Ritonavir, Lopinavir	Carbamazepine
Indinavir	Phenytoin
Nelfinavir	Modafinil
Sequinavir	St. John's Wort
Atazanavir	
Grapefruit/Grapefruit Juice	

Table A3-10: CYP3A Sensitive Substrates

Generic (Trade Name)	
Albendazole (Albenza®)	Levomilnacipran (Fetzima®)
Alfentanil (Alfenta®) - drug has narrow therapeutic index	Lopinavir and Ritonavir (Kaletra®)
Aliskiren (Tekturna®)	Lovastatin (Mevacor®)
Almotriptan (Axert®)	Lurasidone (Latuda®)
Alprazolam (Xanax®)	Maraviroc (Selzentry®)
Aprepitant (Emend®)	Medroxyprogesterone acetate (Depo-Provera®)
Aripiprazole (Abilify®)	Methadone
Avanafil (Stendra®)	Midazolam (Versed®)
Brexpiprazole (Rexulti®)	Mirtazapine (Remeron®)
Bromocriptine (Cycloset®, Parlodel®)	Nevirapine (Viramune®)
Budesonide (Entocort®, Pulmicort®)	Nisoldipine (Sular®)
Buprenorphine (Suboxone®, Butrans®, etc.)	Ospemifene (Osphena®)

Generic (Trade Name)	
Buspirone (Buspar®)	Oxycodone (Percocet®, Oxycontin®)
Cariprazine (Vraylar®)	Paritaprevir (Viekira Pak™, Technivie™) - major substrate
Clonazepam (Klonopin®) (probable)	Pimozide (Orap®) - drug has narrow therapeutic index
Conivaptan (Vaprisol®)	Praziquantel (Biltricide®)
Cyclophosphamide (Cytoxan®)	Propafenone (Rythmol®)
Cyclosporine (Neoral®, Gengraf®, Sandimmune®) - drug has narrow therapeutic index	Quetiapine (Seroquel®)
Daclatasvir (Daklinza™)	Quinidine - drug has narrow therapeutic index
Darifenacin (Enablex®)	Roflumilast (Daliresp®)
Darunavir (Prezista®)	Salmeterol (Serevent®)
Dasatinib (Sprycel®)	Saquinavir (Invirase®)
Diazepam (Valium®)	Sildenafil (Viagra®)
Dienogest (progesterone in oral contraceptives)	Simeprevir (Olysio®)
Dihydroergotamine (DHE-45®, Migranal®) – drug has narrow therapeutic index	Simvastatin (Zocor®)
Dronedarone (Multaq®)	Sirolimus (Rapamune®) - drug has narrow therapeutic index
Drospirenone (progesterone in oral contraceptives)	Suvorexant (Belsomra®)
Elbasvir (Zepatier®)	Tacrolimus (Prograf®) - drug has narrow therapeutic index
Eletriptan (Relpax®)	Tadalafil (Cialis®)
Eplerenone (Inspra®)	Tamsulosin (Flomax®)
Ergotamine (Cafergot®)	Temsirolimus (Torisel®)
Eszopiclone (Lunesta®)	Ticagrelor (Brilinta®)
Ethinyl Estradiol (oral contraceptives, Ortho Evra®, NuvaRing®)	Tinidazole (Tindamax®)
Etonogestrel (Implanon®, Nexplanon®, NuvaRing®)	Tofacitinib (Xeljanz®) (major substrate)
Everolimus (Afinitor®)	Tolvaptan (Samsca®)
Felodipine (Plendil®)	Tipranavir (Aptivus®)
Fentanyl (Duragesic®) - drug has narrow therapeutic index	Triazolam (Halcion®)
Flibanserin (Addyi®) - major substrate	Vardenafil (Levitra®)
Fluticasone (Flovent®, Arnuity Ellipta®)	Verapamil (Calan®, Covera-HS®, Verelan®, etc.)
Grazoprevir (Zepatier®)	Vilanterol (Anoro Ellipta®)
Guanfacine (Intuniv®)	Vilazodone (Viibryd®)
Hydrocodone (Norco®, Vicodin®, etc.)	Vorapaxar (Zontivity®)
Iloperidone (Fanapt®)	Zolpidem (Ambien®)
Indinavir (Crixivan®)	Levomilnacipran (Fetzima®)
Lapatinib (Tykerb®)	Lopinavir and Ritonavir (Kaletra®)

APPENDIX 4. RESPONSE DEFINITIONS FOR B-CELL NHL AND PTCL, CLL, AND CTCL

1. Response Criteria for NHL

Radiographic (including PET scan) and clinical assessments will be evaluated in accordance with The Lugano Classification [4]. The criteria are summarized in Table A4-11.

PET-CT is preferred for FDG-avid lymphomas and CT scan is preferred in other lymphomas. For patients staged with PET-CT, focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, etc.

For patients staged with CT:

- Selection of target (measured) lesions is as follows:
  - Up to 6 of the largest nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters:
  - A measurable node must have a longest transverse diameter of a lesion (LDi) > 1.5 cm.
  - A measurable extranodal lesion (e.g., hepatic nodules) should have an LDi > 1.0 cm.
  - Preferably, nodes should be disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.
  - Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), gastrointestinal (GI) involvement, cutaneous lesions, or those noted on palpation. If possible, they should:
  - Be from disparate regions of the body.
  - Include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Selection of non-target (non-measured) lesions:
  - Any lesions not selected as target (measured) and truly assessable lesions should be considered not measured.
  - These lesions include any nodes, nodal masses, and extranodal lesions not selected as target (measured) or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable lesions, which are any sites of suspected disease that would be difficult to follow quantitatively with measurement, (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, leptomeningeal lesions/disease) and other lesions that cannot be confirmed and followed by imaging.

Table A4-11: Lugano Criteria [4] (Revised Criteria) for Response Assessment in NHL

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 [a] with or without a residual mass on 5PS [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., 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.	Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease.
Nonmeasured lesion Organ enlargement New lesions Bone marrow	Not applicable Not applicable None No evidence of FDG-avid disease in marrow	Absent Regress to normal None Normal by morphology; if indeterminate, IHC negative
Partial Lymph nodes and extralymphatic sites	Partial metabolic response Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size: At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease.	Partial remission (all of the following): > 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. 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 Organ enlargement New lesions Bone marrow	Not applicable Not applicable None 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.	Absent/normal, regressed, but no increase. Spleen must have regressed by > 50% in length beyond normal. None Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
No response or stable disease Target nodes/nodal masses, extranodal lesions	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease < 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 PPD progression:
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or 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
Extranodal lesions		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 (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 15 cm in any axis A new extradnodal 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 New or recurrent lymphoma

5PS = 5-point scale; CT = Computed tomography; FDG = Fluorodeoxyglucose; GI = Gastrointestinal; 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 lesion

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., 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 (e.g., 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 (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] 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.

2. Response Criteria for CLL

Radiographic and clinical assessments in accordance with the criteria established by IWCLL [2] will be used to determine response. CT scan is the preferred method for evaluating tumor response. The spleen and liver should also be assessed by physical examination.

- Selection of target (measured) lesions for imaging or physical examination:
  - Up to six of the largest nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters at baseline.
  - A measurable node must have a longest transverse diameter of a lesion (LDi) > 1.5 cm. A measurable extranodal lesion (e.g., hepatic nodules) should have an LDi > 1.0 cm.
  - 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 (e.g., liver, spleen, kidneys, and lungs), gastrointestinal (GI) involvement, cutaneous lesions, or those noted on palpation.
  - If possible, they should be from disparate regions of the body.
  - If possible, they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Selection of non-target (non-measured) lesions for imaging or physical examination:
  - Any lesions not selected as target (measured) and truly assessable lesions should be considered not measured.
  - These lesions include any nodes, nodal masses, and extranodal lesions not selected as target (measured) or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable lesions, which are any sites of suspected disease that would be difficult to follow quantitatively with measurement, (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, leptomeningeal lesions/disease) and other lesions that cannot be confirmed and followed by imaging.

3. Complete Response (CR)

To satisfy the criteria for CR, all of the following criteria must be met and must persist for ≥ 8 weeks:

- No evidence of new disease
- ALC in peripheral blood of $< 4 \times 10^9$/L
- Regression of all target nodal masses to normal size (i.e., ≤ 1.5 cm in the longest diameter for nodes that were considered large at baseline and ≤ 1.0 cm in the longest perpendicular diameter for nodes that were considered small at baseline)

- Normal spleen and liver size
- Regression to normal of all nodal non-target disease and disappearance of all detectable non-nodal, non-target disease
- No disease-related constitutional symptoms
- Peripheral blood counts meeting all of the following criteria:
  - ANC ≥ 1.5 x 10^9/L without need for exogenous growth factors (e.g., G-CSF)
  - Platelet count ≥ 100 x 10^9/L without need for exogenous growth factors
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

Notes:

- *Morphologically negative bone marrow* is defined as < 30% of nucleated cells and no lymphoid nodules in a bone marrow sample that is normocellular for age.
- Patients who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia that is related to prior or ongoing drug toxicity (and not to CLL) will be considered as a CR with incomplete marrow recovery (CRi).

4. Partial Response (PR)

To satisfy criteria for PR, all of the following criteria must be met and must persist for ≥ *8 weeks:*

- No evidence of new disease
- Decrease in peripheral blood ALC by ≥ 50% from baseline
- A decrease by ≥ 50% from the baseline in the SPD (sum of the products) of the target nodal lesions
- In patients with enlargement of the spleen or liver at baseline:
  - Normal spleen size, or a decrease by ≥ 50% from baseline in the pretreatment enlargement of the vertical dimension below the left costal margin (by palpation) or in total vertical dimension (by imaging)
  - Normal liver size, or a decrease by ≥ 50% from baseline in the pretreatment enlargement of the liver total vertical dimension at the right costal margin (by percussion) or a qualitative decrease in liver size (by imaging)
- No increase in the size of the liver or spleen
- No increase in the size of non-target disease
- No persistent (lasting > 4 weeks) worsening of disease-related constitutional symptoms
- Peripheral blood counts meeting any of the following criteria:

- ANC ≥ 1.5 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (e.g., G-CSF)
- Platelet count ≥ 100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors
- Hemoglobin ≥ 110 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

Note: Patients who achieve a PR by IWCLL 2008 criteria [2] in all parameters except lymphocyte count will be considered PR with lymphocytosis. Patients with a PR with lymphocytosis will not be considered to have achieved a PR until there is a 50% reduction in ALC from baseline was achieved or ALC < 4 × 10^9/L.

Note: Marrow should have at least a 50% reduction in marrow infiltrate or B-lymphoid nodules

5. Stable Disease (SD)

To satisfy the criteria for SD, the following criteria must be met:

- No evidence of new disease, i.e., there is neither sufficient evidence of tumor shrinkage to qualify for PR nor sufficient evidence of tumor growth to qualify for definitive disease progression.

6. Progressive Disease (PD)

- The occurrence of any of the following events indicates definitive PD:
  Evidence of any new disease that was not present as baseline:
- A new node that measures > 1.5 cm in any diameter
- A new node that measures > 1.0 cm to ≥ 1.5 cm in the longest diameter and > 1.0 cm in the longest perpendicular diameter
- New hepatomegaly or splenomegaly
- New non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL)

  Note: Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.

- Evidence of worsening of lymph nodes, spleen or liver, or non-target disease:
  - Increase by ≥ 50% from the nadir in the SPD of target lesions.

- Increase by ≥ 50% from the nadir in the product of the perpendicular diameters for any individual node; progression of a single lesion requires that the lesion demonstrates a ≥50% in the product of its diameters and that the lesion now meets the definition of abnormal (a node that was considered large at baseline must now measure > 1.5 cm in the longest diameter and a node that was considered small at baseline must now measure > 1.0 cm in the longest diameter perpendicular to the long diameter of the lesion).
- Increase by ≥ 50% from the nadir in the longest diameter for any individual node if the node now has a longest perpendicular diameter that is >1.0 cm.
- In a patient with an abnormal spleen, an increase by ≥ 50% from the nadir enlargement of the spleen vertical dimension below the left costal margin (by palpation) or in total vertical dimension (by imaging).
- In a patient with an abnormal liver, an increase by ≥ 50% from the nadir enlargement of the liver total vertical dimension at the right costal margin (by percussion) or a unequivocal qualitative increase in liver size (by imaging).
- Unequivocal increase in the size of non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL).
- Transformation to a more aggressive histology (e.g., Richter syndrome) as established histologically.

7. Treatment-related Lymphocytosis

Treatment-related lymphocytosis, for the purpose of this protocol, is defined as an elevation in blood lymphocyte count of ≥ 50% compared to baseline which occurs in the setting of unequivocal improvement in at least 1 other disease-related parameter including lymph node size, spleen size, hematologic parameters or disease symptoms. Patients with isolated lymphocytosis in the setting of reduced disease burden or improvement in hematologic parameters should not be considered to have progressive disease [2].

8. Response Criteria for Leukemic Forms of Peripheral T-cell Lymphoma (PTCL) (ATLL, PLL, LGL)

A. Response Criteria for ATLL

Table A4-12: Response Criteria for ATLL

Response	Definition	Lymph Nodes	Extranodal Masses	Spleen, Liver	Skin	Peripheral Blood	Bone Marrow
Complete remission*	Disappearance of all disease	Normal	Normal	Normal	Normal	Normal†	Normal
Uncertified complete remission*	Stable residual mass in bulky lesion	≥75% decrease‡	≥75% decrease‡	Normal	Normal	Normal†	Normal
Partial remission*	Regression of disease	≥50% decrease‡	≥50% decrease‡	No increase	≥50% decrease	≥50% decrease	Irrelevant
Stable disease*	Failure to attain complete/partial remission and no progressive disease	No change in size	No change in size	No change in size	No change in size	No change	No change
Relapsed disease or progressive disease	New or increased lesions	New or ≥50% increase§	New or ≥50% increase§	New or ≥50% increase	≥50% increase	New or ≥50% increase#	Reappearance

*Required that each criterion be present for a period of at least 4 weeks.
†Provided that <5% of flower cells remain, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is <4 x 10^9/L.
‡Calculated by the sum of the products of the greatest diameters of measurable disease.
§Defined by ≥50% increase from nadir in the sum of the products of measurable disease.
#Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of >4 x 10^9/L.

Source: NCCN 2018 [77].

B. Response Criteria for PLL

Investigators are encouraged to use the Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia [2] for CLL (Appendix 4-2).

C. Response Criteria for LGL

Response to treatment should be determined by periodic clinical assessments and blood counts (Table A4-13).

Table A4-13: Response Criteria for LGL

Complete Response	The complete normalization of blood counts: • hemoglobin >12 g/dL, platelets >150×10^9/L, absolute neutrophil count >1.5×10^9/L, and lymphocytosis <4×10^9/L, and • a circulating LGL count of <0.5×10^9/L.
Partial Response	An improvement in blood counts: • hemoglobin >8 g/dL, platelets >50\$10^9$/L, and neutrophils >0.5\$10^9$/L, and • the absence of transfusion requirements.
Treatment Failure	Any response not meeting the above criteria within 3 months after the beginning of the treatment.

Source: Bareau, et al [78].

9. Response Criteria for Cutaneous T-Cell Lymphoma (CTCL)

All relevant clinical and radiographic information required to make an assessment should be considered. Nodes/lesions should be selected based on criteria described by Olsen, et al [5].

Table A4-14: Global Response Score

Global Score [a]	Definition	Skin	Nodes, Blood, Viscera
CR	Regression of measurable disease	CR	All categories have CR/NI
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD
		PR	No category has a PD and if any category involved at baseline, at least 1 has a CR or PR
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any
		SD	CR/NI, PR, SD in any category and no category has a PD
PD	Progressive disease	PD	PD in any category
Relapse	Recurrence disease in prior CR		Relapse in any category

CR = Complete response; NI = Noninvolved; PR = Partial response; PD = Progressive disease; SD = Stable disease
Note: It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval during which each patient is under observation also be generated.

Table A4-15: Response in Skin

Response	Definition
CR - Complete Response	100% of skin lesions [a]
PR - Partial Response	50 to 99% clearance of skin disease from baseline without new tumors (T3) in patients with T1, T2, or T4 only skin disease
SD - Stable Disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T3) in patients with T1, T2, or T4 only skin disease, or
PD - Progressive Disease [b]	≥ 25% increase in skin disease from baseline, or New tumors (T3) in patients with T1, T2, or T4 only skin disease, or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

Note: Based on modified Severity Weighted Assessment Tool score.

[a] A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.

[b] Whichever criterion occurs first.

Table A4-16: Response in Lymph Nodes

Response	Definition
CR – Complete Response	All lymph nodes [a] are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR - Partial Response	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm in diameter
SD - Stable Disease	Fails to attain the criteria for CR, PR, and PD
PD - Progressive Disease [b]	≥ 50% increase in SPD from baseline of lymph nodes, or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically, or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N3 histologically

PD = Progressive disease; SPD = Sum of the maximum linear dimension (major axis) x longest perpendicular dimension (minor axis)

[a] Peripheral and central lymph nodes.

[b] Whichever criterion occurs first.

Table A4-17: Response in Viscera

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

PD = Progressive disease; SPD = Sum of the maximum linear dimension (major axis) x longest perpendicular dimension (minor axis)

[a] Whichever criterion occurs first.

Table A4-18: Response in Blood [a]

Response	Definition
CR - Complete Response [b]	B_0
PR - Partial Response [c]	≥ 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2).
SD - Stable Disease	Fails to attain the criteria for CR, PR, and PD.
PD - Progressive Disease [d]	B_0 to B_2, or > 50% increase from baseline and at least 5,000 neoplastic cells/μL, or Loss of response: B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL.
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

[a] As determined by absolute numbers of neoplastic cells/μL.

[b] If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.

[c] There is no PR in those with B1 disease at baseline as the difference within the range of neoplastic cells that define B1 is not considered significant and should not affect determination of global objective response.

[d] Whichever criterion occurs first.

10. Modified Severity Weighted Assessment Tool (mSWAT) for CTCL

D. Total Body Surface Area (TBSA) Involvement by Skin Disease

The body is divided into 12 regions with pre-assigned %TBSA based on the burn literature. The extent of skin disease in each region is quantified by using the patient's palm to measure the %TBSA involvement within region: patient's palm with 4 fingers (excluding the thumb) is 1% of TBSA. Patient's palm without fingers is 0.5% of TBSA. The patient's palm with 4 fingers is traced on a transparency sheet at the baseline visit, using a permanent marker that will not rub off or smear. The transparency of the patient's palm should be used in all mSWAT assessments during the course of the clinical study. The transparency will be labeled with the patient's study ID number kept in the patient's study file on site. Using the baseline visit transparency of the patient's palm, the investigator will measure and record on the electronic case report form (example of table from eCRF is given below) the %TBSA for each lesion type within each of the 12 regions.

E. Severity Weighting Factor

The severity weighting factors will be the following:

1. = patch (flat erythema or erythema with mild infiltration), multiply by 1.
2. = plaque (elevated erythema or erythema with moderate infiltration), multiply by 2.
3. = tumor or ulceration (erythema with fissuring, ulceration or tumor), multiply by 4.

Patch is defined as abnormal skin not elevated from normal skin. A plaque is defined as abnormal skin elevated from normal skin by < 5 mm. A plaque elevated ≥ 5 mm is a tumor.

F. Calculating Skin Scores

The sum of %TBSA by lesion is derived by summing the %TBSA from all regions affected by the lesion. The sum of %TBSA across lesion types (patches, plaques, and tumors) within each region cannot exceed the %TBSA for the region. For example, the %TBSA for the head region is 7%. The sum of %TBSA across lesion types from head can only range from 0 to 7%. The skin score subtotal by lesion type are derived by multiplying the sum of %TBSA for patches from all regions by 1, sum of %TBS of plaques from all regions by 2, and the sum of %TBSA of tumors or ulcers from all regions by 4. The skin score total is derived from summing the skin score subtotals for patches, plaques, and tumors or ulcers. The skin score total is dimensionless with a scale of 0 to 400. See Table A4-19.

Table A4-19: Calculating Skin Scores

Region	% TBSA for the region	% TBSA Patch (or flat erythema)	% TBSA Plaque (or elevated/ indurated erythema)	% TBSA Tumor/Ulceration (or erythema w/fissuring, ulceration)
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
% BSA by Category	100			
Severity Weighting Factor		X 1	X 2	X 4
Skin Score Subtotal				

BSA = Body surface area; TBSA = Total body surface area

Responses will be determined by the criteria described in Table A4-20.

Progression of disease while on treatment should be confirmed by a second assessment 1 to 4 weeks later so that patients who experience a temporary flare of disease due to skin infection or other intercurrent illnesses are not removed from the study prematurely.

Table A4-20: mSWAT Response Assessment

Assessment	Description	Status
Completely Clear	No evidence of disease; 100% improvement	CR
Marked Improvement	Greater than or equal to 50% decrease in skin scores compared to baseline and improvement is maintained for 4 weeks	PR
Slight Improvement	Less than 50% decrease in skin scores compared to baseline	SD
Worse	≥ 25% increase in skin scores compared to baseline while the patient is actively taking the study drug *or* ≥ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patent is actively taking the study drug.	PD

CR = Complete response; PD = Progressive disease; PR = Partial response; SD = Stable disease

APPENDIX 5. PROGNOSTIC FACTORS [19]

The following prognostic indices are presented: Follicular Lymphoma International Prognostic Index (FLIPI, Table A5-21), International Prognostic Index (Table A5-22), and Age-Adjusted Prognostic Index (Table A5-23), and Simplified Mantle-Cell Prognostic Index (MIPI) (Table A5-24).

Table A5-21: Follicular Lymphoma International Prognostic Index -1 (FLIPI-1) Criteria

Age	**≥ 60 years**
Ann Arbor Stage	III-IV
Hemoglobin Level	< 12 g/dL
Serum LDH Level	> ULN
Number of Nodal Sites	≥ 5
Risk Group According to FLIPI Chart	
	Number of Factors
Low	0-1
Intermediate	2
High	≥ 3

FLIPI-1 = Follicular Lymphoma International Prognostic Index;
LDH = Lactic dehydrogenase; ULN = Upper limit of normal

Table A5-22: International Prognostic Index (IPI)

All Patients	**International Index, All Patients**	
Age ≥ 60 Years	Low	0 or 1
Serum LDH > Normal	Low-intermediate	2
Performance Status 2-4	High-intermediate	3
Stage III or IV	High	4 or 5
Extranodal Involvement > 1 Site		

LDH = Lactic dehydrogenase; ULN = Upper limit of normal

Table A5-23: Age-Adjusted International Prognostic Index

Patients ≤ 60 Years of Age	**International Index, ≤ 60 Years of Age**	
Stage III or IV	Low	0
Serum LDH > normal	Low-intermediate	1
Performance Status 2-4	High-intermediate	2
	High	3

LDH = Lactic dehydrogenase; ULN = Upper limit of normal

Table A5-24: Simplified Mantle-Cell Prognostic Index (MIPI) [79]

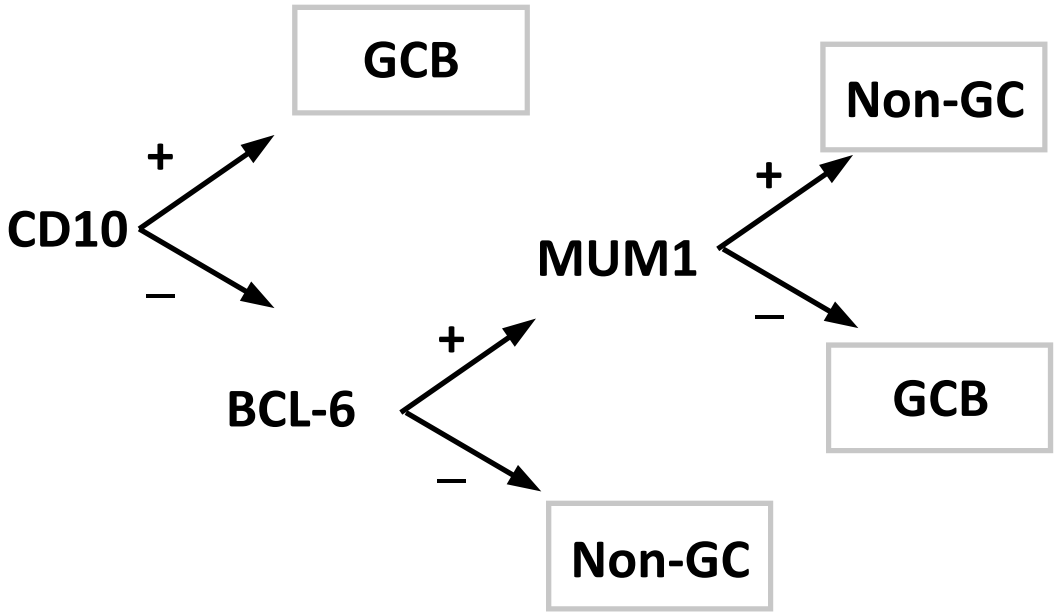
Points	Age in Years	ECOG Status	LDHULN	WBC, 10^9/L
0	< 50	0-1	< 0.67	< 6.700
1	50-59	Not Applicable	0.67–0.99	6.700–9.999
2	60-69	2-4	1.000–1.49	1.000–14.999
3	≥ 70	Not Applicable	≥ 1.5000	≥ 1.5000

ECOG = Eastern Cooperative Oncology Group; LDH = Lactic dehydrogenase; ULN = Upper limit of normal; WBC = White blood cell

Note: For each prognostic factor, 0 to 3 points were given to each patient, and points were summed up to a maximum of 11. Patients with 0 to 3 points n summary were classified as low risk, patients with 4 to 5 points as intermediate risk, and patients with 6 to 11 points has high risk. ECOG performance status was weighted with 2 points if patients were unable to work or bedridden (ECOG 2–4). LDH was weighted according to the ratio to the ULN. Thus, for a ULN of 240 U/L, the cutpoints were 180 U/L, 240 U/L, and 360 U/L, for example.

APPENDIX 6. DIFFERENTIAL OF ABC VS. GCG TYPE OF DLBCL BY IHC-HANS METHODOLOGY

Figure A6-5: Decision Tree for Immunoperoxidase Tissue Microarray (TMA) [75]



DLBCL = Diffuse large B-cell lymphoma; GCB = Germinal center B-cell–like (a subclassification of DLBCL); non-GC = Non-germinal cell

APPENDIX 7. STAGING SYSTEMS FOR CLL AND NHL [4, 19]

The Rai and Binet staging systems for CLL are presented Table A7-25 and Table A7-26, respectively. The Lugano Modification of the Ann Arbor Guidelines is presented in Table A7-27.

Table A7-25: Rai Staging System for Chronic Lymphocytic Lymphoma

Rai Stage	Description	Risk Factor
0	Lymphocytosis and no enlargement of the lymph nodes, spleen, or liver, and with near normal red blood cell and platelet counts.	Low Risk
I	Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged and the red blood cell and platelet counts are near normal.	Intermediate Risk
II	Lymphocytosis plus an enlarged spleen (and possibly an enlarged liver), with or without enlarged lymph nodes. The red blood cell and platelet counts are near normal.	Intermediate Risk
III	Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal.	High Risk
IV: Liver	Lymphocytosis plus thrombocytopenia (too few blood platelets), with or without anemia, enlarged lymph nodes, spleen, or liver.	High Risk

Table A7-26: Binet Staging System for Chronic Lymphocytic Lymphoma

Binet Stage	Description
A	Fewer than 3 areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
B	3 or more areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
C	Anemia and/or thrombocytopenia are present.

Table A7-27: Lugano Modification of Ann Arbor Staging System (for Primary Nodal Lymphomas)

Stage	Involvement	Extranodal "E" Status
Limited		
Stage I	One node or group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	2 or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II "bulky" [a]	Stage II as above with "bulky" disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm	Not applicable
	Nodes above the diaphragm with spleen involvement	
Stage IV	Additional non-contiguous extralymphatic involvement	Not applicable

CT = Computed tomography; PET = Positive-emission tomography

Notes: Extent of disease is determined by PET-CT for avid lymphomas and CT for non-avid lymphomas. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue. Categorization "A" or "B" has been removed from the Lugano Modification of Ann Arbor Staging.

[a] Whether stage II bulky disease is treated a limited or advanced disease may be determined by histology and a number of prognostic factors.

APPENDIX 8. GLOBAL HEALTH ASSESSMENT

To be completed by the patient. Patient may decline to answer.

Circle the number that best represents your level of health today.

0 means the worst state of health you can imagine

10 means the best state of health you can imagine

Worst State of Health										Best State of Health
0	1	2	3	4	5	6	7	8	9	10

(_) decline to answer

APPENDIX 9. COCKCROFT-GAULT METHOD FOR EVALUATING CREATININE CLEARANCE [80]

For serum creatinine concentration in mg/dL:

CrCl = (140-age+) × (wt) x 0.85 (if female), or × 1.0 (if male)

(mL/min) 72× serum creatinine (mg/dL)

For serum creatinine concentration in µmol/L:

CrCl = (140-age+) × (wt) × 0.85 (if female), or × 1.0 (if male)

(mL/min) 0.81 × serum creatinine = (µmol/L) + age in years, weight (wt) in kilograms

CrCl = Creatinine clearance; wt = Weight

APPENDIX 10. LIKERT SCALE

Likert Scale for Pruritus Evaluation

To be completed by patient.

No Itch										Worst Itch Imaginable
0	1	2	3	4	5	6	7	8	9	10

Circle the number that best represents your level of itching.

(_) decline to answer

APPENDIX 11. T-CELL LYMPHOMA CLASSIFICATIONS

Table A11-28: Mature T- and NK-cell Neoplasms in the 2008 WHO Classification of Lymphoid Tumors [81]

Leukemic or Disseminated	T-cell prolymphocytic leukemia
	T-cell large granular lymphocytic leukemia
	Chronic lymphoproliferative disorders of NK cells [a]
	Aggressive NK-cell leukemia
	Adult T-cell lymphoma/leukemia (HTLV1-positive)
	Systemic EBV-positive T-cell lymphoproliferative disorders of childhood
Extranodal	Extranodal NK/T-cell lymphoma, nasal type
	Enteropathy-associated T-cell lymphoma
	Hepatosplenic T-cell lymphoma
Cutaneous	Mycosis fungoides
	Sézary syndrome
	Primary cutaneous CD30_ lymphoproliferative disorders
	Primary cutaneous anaplastic large cell lymphoma
	Lymphomatoid papulosis
	Subcutaneous panniculitis-like T-cell lymphoma
	Primary cutaneous gamma-delta T-cell lymphoma
	Primary cutaneous aggressive epidermotropic CD8_ cytotoxic
	T-cell lymphoma [a]
	Primary cutaneous small/medium CD4_ T-cell lymphoma [a]
	Hydroa vacciniforme-like lymphoma
Nodal	Angioimmunoblastic T-cell lymphoma
	Anaplastic large cell lymphoma, ALK-positive
	Anaplastic large cell lymphoma, ALK-negative
	Peripheral T-cell lymphoma, not otherwise specified

[a] Provisional entity.