STATISTICAL ANALYSIS PLAN

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Sponsor:	Portola Pharmaceuticals, a subsidiary of Alexion 270 East Grand Avenue, Suite 22 South San Francisco, CA 94080, USA
Study 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)
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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BID	Bis in die (twice a day)
BOR	Best overall response
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
DLT	Dose limiting toxicity
DOR	Duration of response
eCRF	Electronic case report form
FL	Follicular lymphoma
IV	Intravenously
KM	Kaplan-Meier
MAD	Maximum administered dose
MTD	Maximum tolerated dose
MRD	Minimum residual disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PTCL	Peripheral T-cell lymphoma
QD	Quaque die (once a day)
SD	Stable disease
SLL	Small lymphocytic lymphoma
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the detailed plans for the analysis of safety and efficacy data for Study 13-601. This document is based on Protocol Amendment #9 dated 29-October-2019. This analysis plan does not include pharmacokinetics, pharmacodynamics, minimum residual disease, and exploratory biomarker analyses, which will be separate reports.

This version of SAP (v2.0) is an amendment to the original SAP (v1.0) dated 23 July 2015 (developed by Sarah Cannon Research Institute Development Innovations on behalf of Portola Pharmaceuticals, Inc) prior to Protocol Amendment #4, which initiated the change in the study design from a phase 1 dose escalation study to a phase 1/2a study. No formal statistical analyses and clinical study report (CSR) were done based on the original version of SAP (v1.0) for the phase 1 portion of the study. There have been 5 additional protocol amendments after Protocol Amendment #4, therefore, the purpose of this version of SAP (v2) is to provide a unified plan for analysis of both phase 1 and phase 2a portions of the study as basis for a combined clinical study report (CSR).

2. STUDY OVERVIEW

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

In the Phase 2a dose expansion portion, patients will be enrolled in one of 6 disease cohorts. 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.

3. STUDY OBJECTIVES

3.1. Phase 1 Objectives (Dose Escalation)

3.1.1. 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).

3.1.2. 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.

3.2. Phase 2a Objectives (Dose Expansion/Exploratory)

3.2.1. 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.

3.2.2. 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.

4. STUDY ENDPOINTS

4.1. Phase 1 Endpoints

4.1.1. Primary Endpoint
• The primary safety endpoint will be the incidence of Dose-limiting toxicity (DLT) by dose level.

4.1.2. Secondary Endpoints
• ORR, defined as the proportion of subjects achieve partial response (PR) or better

• Clinical benefit rate, defined as the proportion of subjects achieve stable disease or better

• Progression-free survival (PFS), defined as the time from the start of study treatment to the first documentation of disease progression as assessed by investigator or death from any cause, whichever occurs first.

• Duration of response (DOR), defined as the time from the date of the earliest PR or better to the first documentation of disease progression or death from any cause, whichever occurs first.

• Adverse event profile 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.

4.2. Phase 2a Endpoints

4.2.1. Primary Endpoint
• The primary efficacy endpoint is ORR

4.2.2. Secondary Endpoints
• Duration of response (DOR), progression-free survival (PFS), time to treatment response (TTR), and dominant mass response (target nodal and extra-nodal mass response).

• Clinical benefit rate

• Adverse event profile

• Clinically significant changes in vital signs, physical exams

• Changes in hematology and chemistry laboratory parameters.

• PD endpoints: Changes in biomarker data for a range of ex vivo assays.

4.2.3. 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.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Phase 1 Sample Size

The sample size is based on clinical judgment and is typical of studies of this type. 43 subjects were enrolled in the phase 1 part of the study.

5.2. 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 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 of section 3.1.2 of the protocol.

6. ANALYSIS POPULATIONS

The safety analysis population will consist of all patients treated with at least 1 dose of study medication (cerdulatinib or rituximab). The safety analysis population will be used for all safety analyses. Subjects disposition, demographics, baseline characteristics, and treatment exposure will also be analyzed based on the safety analysis population.

The efficacy analysis population will consist of all patients who have taken at least 1 dose of study medication and have had at least 1 post-baseline investigator response assessment (IRA). The efficacy analysis population will be used for the primary and secondary efficacy endpoints for the follicular lymphoma (FL) patients in Cohort 1 and 2 and the peripheral T-cell lymphoma (PTCL) patients in Cohort 5. In addition, efficacy will also be assessed in the corresponding safety analysis population in Cohort 1, 2, and 5.

7. STATISTICAL METHODS

7.1 Data Analysis General Considerations

Where applicable, descriptive statistics will be provided. For continuous variables, n, mean, standard deviation (SD), median, minimum, and maximum will be presented. For discrete variables, the frequency and percentage will be presented. For time to event variables, unless specified otherwise, the Kaplan-Meier (KM) estimate and corresponding two-sided 95% confidence intervals (CIs) will be presented for the median and quartiles and, as necessary, for the event-free rates at the selected time points.

All calculations and analyses will be performed using SAS version 9.4 or higher.

Unless specified otherwise, the Phase 1 portion will be summarized by the initial assigned dose level and the Phase 2a portion will be presented by cancer type. Summaries and analyses will be done for Phase 1 and Phase 2a separately. There will be no pooling of Phase 1 and Phase 2a data. For the subjects enrolled in Phase 1 but continued in Phase 2a, only baseline information (baseline demography, disease characteristics, and prior anti-cancer therapies) from Phase 1 database will be used for corresponding Phase 2a summary tables, all other data will remain separate in Phase 1 and Phase 2a summary tables unless specified otherwise.

7.1.1. Definitions and Computations

Study treatment (study drug): cerdulatinib or rituximab

Study day: study day will be calculated relative to the date of the first dose of study treatment.

Treatment duration: date of last dose of study treatment – date of first dose of study treatment +1

Baseline: unless otherwise specified, a baseline value is defined as the last non-missing value collected on or before the first dose of study treatment (i.e. on/before Cycle 1 Day 1)

7.1.2. Handling of Missing Data

Missing data will not be imputed unless otherwise specified. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures as provided in Appendix A.

When summarizing discrete variables, subjects with missing data are generally included in the denominator to calculate percentage unless otherwise specified. In general, a category of "Missing" will be created and the subjects with missing data will be presented.

When summarizing continuous variables, subjects with missing data are not included in calculations unless otherwise specified.

No imputation of AE grades will be performed. AEs with missing CTCAE grades will only be summarized in the all-grade column. If the assessment of the relationship of an AE to study treatment is missing, the AE is assumed to be related to the study treatment in the summary tables. No imputation will be done in the AE listings.

The reason for lack of sufficient information for response evaluation for FL and PTCL subjects in Cohorts 1, 2, and 5 will be listed with reasons for end of treatment/study, death, and any subsequent anti-cancer therapy if applicable.

7.2. Subject Disposition

The following subject disposition information will be summarized:

- Number of subjects treated
- Number and percentage of treated subjects who discontinued treatment
- Primary reason for treatment discontinuation

The number of subjects treated will be summarized by site. Due to inconsistencies in different versions of protocol and data entry instructions in study follow-up, the number of subjects who discontinued study will not be summarized.

7.3. Protocol Deviations

Protocol deviation criteria, types, and classification designations (major vs minor protocol deviations) are defined in the protocol deviation management plan. Protocol deviations are documented and reviewed throughout the study in accordance to the protocol deviation management plan. The list of protocol deviations and their classifications will be finalized prior to the database lock. Final major protocol deviations will be summarized by type and all protocol deviations (both major and minor) will be listed.

7.4. Demographics and other baseline characteristics

If applicable, the following demographic and baseline characteristics will be summarized for Phase 1 portion and Phase 2a portion, respectively.

- Age (years)
- Age group (<=65 vs >65 but <=75 vs >75)
- Sex
- Ethnicity
- Race
- Weight
- ECG overall result
- ECOG performance status
- Hemoglobin
- Absolute neutrophil count
- Platelet count
- IgG level

- Amylase
- Lipase
- Lymphocyte count
- AST
- ALT
- Creatinine Clearance

In addition, the following disease history and characteristics will be summarized for the follicular lymphoma (FL) patients in Cohort 1 and 2 only.

- Time since initial diagnosis (month)
- Time since the most recent progression (month)
- Baseline bone marrow involvement (Yes vs No)
- Relapsed vs refractory
- Bulky disease (any target lesion with >=7cm in the longest diameter or at least 3 target lesions with >=3cm in the longest diameter: Yes vs No)
- Prior stem cell transplant (Yes vs No)
- Prior radiotherapy (Yes vs No)
- Ann Arbor stage III/IV (Yes vs No)
- Serum lactate dehydrogenase >ULN (Yes vs No)
- Follicular Lymphoma Internal Prognosis Index (FLIPI-1 score)

7.5. Prior systemic anti-cancer therapy

For the FL patients in Phase 2a Cohort 1 and 2 and PTCL patients in Phase 2a Cohort 5 only, the number of prior regimens will be summarized numerically and categorically. Best overall response to the last regimen and time since the end of last regimen will be summarized descriptively. The therapies with the same regimen number are counted as one line of prior therapy.

In addition, the types of prior systemic anti-cancer regimens will be internally adjudicated and summarized for the FL patients in Phase 2a Cohort 1 and 2 and PTCL patients in Phase 2a Cohort 5.

Prior anti-cancer therapies for other subjects except FL subjects in Phase 2a Cohort 1 and 2 and PTCL patients in Phase 2a Cohort 5 will be listed only.

7.6. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 16.1 for Phase 1; version 21.1 for Phase 2a or higher). The number and percentage of subjects reporting a history of any medical condition, as recorded in the eCRF, will be summarized by system organ class (SOC) and preferred term (PT).

7.7. Prior and concomitant medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (version SEPTEMBER 2013 for Phase 1; version B2 Sep2018 for Phase 2a or higher) and further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

Prior medications are defined as medications that started before the first dose date.

Concomitant medications are defined as medications that (1) started before the first dose of the study treatment and were continuing at the time of the first dose of the study treatment, or (2) were started on or after the first dose date of the study treatment up to 30 days after the last dose date.

The number and percentage of subjects reporting prior medication and concomitant medications will be summarized by ATC medication class level 2 and WHO drug preferred term.

7.8. Efficacy analysis

The efficacy of the Phase 1 patients will be presented in the subject listing only. For Phase 2a patients, efficacy will be summarized and analyzed for the FL patients in Cohort 1 and 2 and the PTCL patients in Cohort 5 only. For FL subjects in Cohort 1 and 2, efficacy will be summarized by number of prior regimens (<=3 vs >=4). Efficacy of PTCL will be summarized by pathology subgroup as defined in Appendix B (AITL/TFH vs NOS vs Others). The efficacy listing will be provided for non-FL/non-PTCL patients in Cohort 1, 3, 4, and 6.

All efficacy analyses will be based on the efficacy analysis population. The efficacy analyses will also be analyzed in the corresponding safety analysis population in Phase 2a Cohort 1, 2, and 5 as sensitivity analyses.

7.8.1. Primary Efficacy Endpoint

Overall response rate (ORR) is defined as the proportion of subjects who achieve partial response (PR) or better as the best overall response (BOR) per Lugano criteria (Cheson, 2014, see appendix C) as assessed by the investigator. BOR is defined as the best response from treatment start to the data cutoff date (inclusive), disease progression (inclusive), or the start of new anti-cancer therapies (inclusive), whichever occurs first.

ORR will be calculated by cohort, and the associated 95% exact confidence interval (CI) will be estimated using the Clopper-Pearson method.

The primary endpoint of ORR may also be analyzed in additional subgroups of the efficacy analysis population as sensitivity analysis.

7.8.2. Secondary Efficacy Endpoint

7.8.2.1. Progression free survival

Progression-free survival (PFS) is defined as the time from the start of study treatment to the first documentation of disease progression as assessed by investigator (see appendix C) or death from any cause, whichever occurs first.

Progression-free survival = (first documentation of disease progression or death – first dose date of study treatment + 1) /30.4375 in months.

PFS will be right censored for subjects who meet one of the following conditions: 1) no baseline disease assessments; 2) starting a new anti-cancer therapy before documented disease progression or death; 3) progression or death immediately after more than 6 months since the last disease assessment (or more than 12 months if beyond cycle 12); and alive without documented disease progression. The censoring convention follows the FDA guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018) and references within the guidance document. The censoring rules are summarized in Table 1.

Table 1. Date of Event or Censoring for PFS

Scenario	**Date of PFS Event or Censoring**	**Outcome**
Death or progression between the planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Event
Death before the first disease assessment	Date of death	Event
No baseline disease assessment	Date of first dose of study treatment	Censored
New anti-cancer treatment started	Date of last disease assessment prior to or on the date of new anti-cancer treatment	Censored
Death or progression immediately after missing more than 1 scheduled disease assessment [1]	Date of the last disease assessment before death or progression	Censored
Alive without documented disease progression	Date of last disease assessment	Censored

[1] missing >=6 months if in Cycle 1~12 or missing >=12 months if beyond Cycle 12

The distribution of PFS, including median and the PFS rate at selected time points (e.g. 12 months), will be estimated using the Kaplan-Meier method. The 95% CI for the median and the quartiles of PFS will be estimated using the Brookmeyer method (Brookmeyer 1982). The 95% CI for the PFS rate at the selected time points will be estimated using the Greenwood formula (Greenwood 1926). The duration of PFS follow-up will be estimated using the reverse Kaplan-Meier method (Schemper and Smith 1996). The Kaplan-Meier curve for PFS will be plotted for Cohort 1 and 2 FL patients, respectively.

7.8.2.2. Duration of response

For responders (PR or better), duration of response (DOR) is defined as the time from the date of the earliest PR or better to the first documentation of disease progression or death from any cause, whichever occurs first. The censoring convention and analysis method of DOR will be the same as those for PFS in Section 7.8.2.1. DOR will be analyzed for subjects who achieved PR or better (i.e. responders only).

DOR = (first documentation of progression or death – the date of the earliest PR or better + 1) /30.4375 in months.

7.8.2.3. Time to response

For responders (PR or better), time to response (TTR), defined as the time (in month) from the start of study treatment to the date of the earliest PR or better, will be summarized using descriptive statistics for a continuous variable. TTR will not be analyzed using the Kaplan-Meier method for time to event endpoints.

7.8.2.4. Clinical benefit rate

Clinical benefit rate (CBR) is defined as the proportion of subjects who achieve stable disease (SD) or better as the best overall response (BOR) per Lugano criteria (Cheson, 2014) as assessed by the investigator. The summary and analysis method of CBR will be the same as those for ORR as described in Section 7.8.1.

7.8.2.5. Dominant mass response rate

Dominant mass response rate is defined as the proportion of patients who achieve a >=50% decrease from baseline in the sum of products of the greatest perpendicular diameters (SPD) of the target nodal and extra-nodal lesions. The summary and analysis method of dominant mass response rate will be the same as those for ORR as described in Section 7.8.1.

7.8.2.6. Lymphadenopathy

Tumor burden in lymph nodes as measured by target nodal lesions from CT scans will be plotted in terms of waterfall plot SPD (sum of product of diameters). The best percentage improvement in target nodal lesion SPD will be plotted against subjects. New lesion will not be included in the waterfall plot calculation.

Best % improvement in SPD = (lowest post-baseline SPD of target nodal lesions–baseline SPD of target nodal lesions)/baseline SPD of target nodal lesions X 100%.

7.8.3 Subgroup Analysis

As appropriate (e.g. when there are sufficient number of subjects in the subgroup), the primary efficacy endpoint and selected secondary endpoints will be summarized in the following subgroups for the FL patients in Phase 2a Cohort 1 and 2 and the PTCL patients in Phase 2a Cohort 5:

- Age group (<=65 vs >65)
- Sex
- Prior lines of systemic anti-cancer therapy (<=3 vs >=4)
- Baseline ECOG performance score (0 vs >=1)
- Baseline bone marrow involvement (Yes vs No)
- Relapsed vs refractory
- Bulky disease (any target lesion with >=7cm in LDi or at least 3 target lesions with >=3cm LDi: Yes vs No)
- Follicular Lymphoma Internal Prognosis Index (FLIPI score, FL patients only)

7.9. Safety Analysis

All safety analyses will be performed in the safety analysis population.

Safety will be primarily assessed on the basis of adverse events (AE) rates. Clinical laboratory data, ECG findings, physical examinations, and vital signs will also be used for determining safety. Descriptive statistics will be used to summarize the safety data. The Phase 1 portion will be summarized by the initial assigned dose level and the Phase 2a portion will be presented by cancer type.

7.9.1 Treatment Exposure and Compliance

Extent of exposure to study drugs will be summarized descriptively as the number of cycles started, duration of treatment, duration of treatment without full-day dose interruption (defined as full-day with 0 mg dose actually taken), cumulative total dose per subject, actual dose intensity and relative dose intensity.

The number and percentage of subjects with dose reductions, dose interruptions, dose interruptions >= 3 days that are not immediately followed by the end of treatment due to disease progression, and drug discontinuation will be tabulated, and the primary reason for dose modifications will be summarized.

The actual dose intensity (mg/day) is defined as the actual cumulative dose (mg) taken based on the total dose per day divided by treatment duration. The relative dose intensity (RDI) is defined as the ratio of actual dose intensity to the planned dose intensity (i.e. the initial assigned dose level in mg/day) in percentage.

Time to first occurrence of dose reduction/interruption due to an AE will be summarized descriptively. In addition, time to treatment failure, defined as time from start of study treatment to discontinuation of study treatment due to any reason, will be summarized.

7.8.1. Adverse Events

Summary tables and listings will be provided for all reported treatment emergent adverse events (TEAEs), defined as AEs that start on or after the first day of any study drug that is administered and within 30 days of the last administration of any study drug. Missing and partially missing AE start dates will be imputed according to the specification described in Appendix A. The reported AE will be coded using MedDRA (version 16.1 for Phase 1; version 21.1 or higher for Phase 2a). AEs severity grading scales in Phase 1 are based on the NCI CTCAE version 4.03. For AEs in Phase 2a, AE severity grades are mixture of grading scales of the NCI-CTCAE version 4.03 and the NCI CTCAE version 5. No imputation of AE grades will be performed. AE with missing CTCAE grade will only be summarized in the all-grade column.

The causal relationship between the occurrence of an AE and each treatment will be assessed by the investigator. For summary of related AEs, causality assessment by the investigator per eCRF will be mapped based on Table 2. If the assessment of the relationship of an AE to study treatment is missing, the AE is assumed to be related to the study treatment in the table summary. No imputation will be done in the AE listings.

Table 2. Causality Mapping of AEs

Relationship to Study Drug per Investigator	**Summary of AEs**
Unrelated	Not related
Unlikely	Not related
Possible	Related
Probable	Related

TEAEs will be summarized based on the number and percentage of subjects experiencing AEs. When summarizing TEAEs by MedDRA system organ class (SOC) and preferred term (PT), a subject reporting the same AE more than once will be counted only once when calculating the incidence 1) within a given SOC, and 2) within a given SOC-PT combination. Similarly, a same AE will be counted only once within a PT when summarizing by PT only. In both situations, the maximum CTCAE toxicity grade and the strongest causal relationship to the study drug for such events will be used.

Tabular summaries of the following will be provided:

- TEAEs by PT
- TEAEs by SOC, PT
- TEAEs by SOC, PT, and maximum severity grade
- Grade 3 or higher TEAEs by PT
- Grade 3 or higher TEAEs by SOC, PT
- Grade 3 or higher TEAEs by SOC, PT and maximum severity grade
- Cerdulatinib-related TEAEs by PT
- Cerdulatinib-related TEAEs by SOC, PT
- Cerdulatinib-related TEAEs by SOC, PT, and maximum severity grade
- Rituximab-related TEAEs by PT (Cohort 2 only)
- Rituximab-related TEAEs by SOC, PT (Cohort 2 only)
- Rituximab-related TEAEs by SOC, PT, and maximum severity grade (Cohort 2 only)
- Serious TEAEs by PT
- Serious TEAEs by SOC, PT
- TEAEs leading to cerdulatinib discontinuation by PT
- TEAEs leading to cerdulatinib discontinuation by SOC, PT
- TEAEs leading to cerdulatinib reduction by PT
- TEAEs leading to cerdulatinib reduction by SOC, PT
- Fatal TEAEs by PT
- Fatal TEAEs by SOC, PT.

TEAEs leading to rituximab dose modifications and discontinuations will be listed only.

Summaries (all-grade and grade 3 or above) will be provided for cytopenia category by combining following preferred terms in the AE dataset:

- Neutropenia: neutropenia, neutrophil count decreased, febrile neutropenia
- Thrombocytopenia: thrombocytopenia, platelet count decreased
- Anaemia: anaemia.
- Leukopenia: leukopenia, white blood cell count decreased
- Lymphopenia: lymphopenia, lymphocyte count decreased

For the following categories of TEAEs of special interest, the time to the first onset of the event will be analyzed (e.g. median/mean and min/max).

- All-grade gastrointestinal disorders of special interest
- Grade 3 or higher gastrointestinal disorders of special interest
- All-grade infections of special interest (lower respiratory bacterial infections)
- Grade 3 or higher infections of special interest (lower respiratory bacterial infections)

The relationship between all-grade infections of interest and concomitant compliance use of antimicrobial prophylaxis will be explored. In addition, gastrointestinal disorders and infections of special interest may be analyzed for certain population subgroups as appropriate.

In addition, selected safety summaries will be repeated for the subset of phase 2a subjects with 30 mg BID as starting cerdulatinib dose.

A summary of the number of deaths and the primary cause of death, classified by deaths within 30 days of last dose of study drug and deaths beyond 30 days after the last dose, will be provided.

7.8.1.1. Dose limiting toxicity in Phase 1

The number and percentage of patients experiencing dose limiting toxicities as captured in the eCRF by the investigator during Phase 1 will be summarized by initial dose cohort.

DLT is 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.

7.8.2. Laboratory Values

Summary tables will include descriptive statistics for the actual values and changes from baseline by scheduled time points in selected hematology, serum chemistry, and coagulation test results.

The incidence of potential Hy's law cases, identified as ALT/AST > 3 x ULN (upper limit of normal) and total bilirubin > 2 x ULN, will be summarized.

All parameters will be converted to consistent units according to the International System of Units before summarization.

All clinical laboratory results will be listed by subject and timing of collection.

7.8.3. Vital Signs

Summary tables for vital signs and their change from baseline will be presented for each scheduled time point by cohort. All vital sign data will be listed by subject and time of measurement.

7.8.4. Electrocardiogram (ECG)

The number and percentage of subjects with 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant' ECG results will be summarized at baseline and each post-baseline time point.

All ECG data will be listed by subject and time of measurement.

The actual value of QTcF at each time point and change from baseline at each post-baseline time point will be summarized by cohort. Additionally, the number and percentage of subjects in each treatment group who meet any of the following criteria for QTcF will be tabulated.

- Maximum value > 450 to 480 msec
- Maximum value > 480 to 500 msec
- Maximum value > 500 msec
- Maximum increase from baseline > 30 to 60 msec
- Maximum increase from baseline > 60 msec

7.8.5. Physical Exam

Physical examination results including liver and spleen assessments will be listed for all subjects.

7.9. Other Analyses

7.9.1. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Performance Status will be performed pre-dose on Cycle 1 Day 1, Cycle 2 Day 1, every 3 cycles (3, 6, 9, 12+) Day 1 and 30 days post-last treatment. The number and percentage of subjects in each category will be summarized at each visit by cohort. All results will be listed.

7.9.2. Global Health Assessments

Global Health Assessments will be performed pre-dose on Cycle 1 Days 1, 8 and 15, Cycle 2 Day 1, every 3 cycles (3, 6, 9, and 12+) Day 1, and 30 days post-last treatment. The Global Health Assessment asks patients to rate their level of health today on a scale of 0 (the worst state

of health you can imagine) to 10 (the best state of health you can imagine). Descriptive statistics for Global Health Assessments score at each visit and the change from baseline at each post-baseline visit will be summarized at each visit and the change from baseline at each post-baseline visit by cohort. All data will be listed.

8. CHANGES IN THE PLANNED ANALYESE

There are several changes in this version of SAP (v2.0) from the analyses specified in the protocol (amendment #9 dated 29-Oct-2019) due to data limitations as documented in the 13-601 Study Data Handling Document.

Most importantly, aggregated analyses of efficacy data are only limited to Phase 2a Cohort 1/2 FL patients and Cohort 5 PTCL patients. Efficacy data of all other patients will be for listing purposes only. In addition, lymph node response as a secondary endpoint in phase 2a is changed to dominant mass response in order to include both nodal and extra-nodal target lesions as measure of tumor burden.

In addition, AE severity grades in Phase 2a AE by grade analyses are mixture of the NCI CTCAE version 4.03 grading scales and the NCI CTCAE version 5.0 grading scales.

9. REFERENCES

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Food and Drug Administration (2018). Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Greenwood, M. (1926) The Natural Duration of Cancer. Public Health and Medical Subjects, 33: 1-26.

Schemper M, Smith TL. (1996) A note on quantifying follow-up in studies of failure time. Control Clin Trials. 17(4): 343-346.

APPENDIX

A. Imputation of Missing or Partially Missing Dates

In general, missing or partial dates will be imputed at the data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

1. Prior/Concomitant Medications

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant. The following rule will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to Jan 01
- If only day is missing, then set to the 1st of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to Dec 31
- If only day is missing, then set to the last day of the month

If start/end date of a medication is completely missing, do not impute.

2. Adverse Events

When the start/end date of an AE is partially missing, the date will be imputed to determine whether the AE is treatment-emergent. When unable to determine, the AE will be considered as treatment emergent by default. The following rules will be applied to impute partial dates for AEs:

If start date of an AE is partially missing, impute as follows:

- If both month and day are missing, the imputed value will be Jan 1 or the first dosing date if they have the same year, whichever is later.
- If only day is missing, the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.
- If start date is completely missing, the imputed day will be the first dosing date as long as the AE end date is not before the first dosing date.

If the end date of an AE is partially missing, impute as follows:

- If both month and day are missing, the imputed value will be Dec 31
- If only day is missing, the imputed day will be the last day of the month
- If end date is completely missing, do not impute

3. Deaths

In case complete death dates are not recorded, impute as follows:

- If both month and day are missing, the imputed value will be Jan 1 or the last date of subject known to be alive+1, whichever is later.
- If only day is missing, the imputed value will be 1st of the month or the last date of subject known to be alive+1, whichever is later.

4. Subsequent Anti-cancer therapy

If the start day of a subsequent anti-cancer therapy is missing, it will be assumed to be the first day of the month.

5. Cancer Diagnosis

If a cancer diagnosis date is partially missing, impute as follows:

- If both month and day are missing, the imputed value will be Jan 1
- If only day is missing, the imputed day will be the first day of the month
- If end date is completely missing, do not impute

6. Prior Therapy/Response to Prior Therapy

If the day of a prior therapy or response to prior therapy date is missing, set it to 15th of the month. Otherwise, do not impute.

B. Pathology subgroup of Peripheral T-cell Lymphoma (PTCL)

CSR TFL Column	Pathology in EDC
AITL/TFH	AITCL
	PTCL Angioimmunoblastic T-Cell Lymphoma (AITL)
	PTCL with T-follicular helper phenotype
NOS	PTCL (Peripheral T-Cell Lymphoma) -NOS
Others	ATLL
	ATTL
	ATLL, HTLV-1 associated
	CD4+ PTCL, skin only
	CD4+ PTCL, skin-only
	Cutaneous Gamma Delta
	Cutaneous gamma-delta T-cell Lymphoma
	G/D TCL, skin and LN+
	HTLV-1 ATLL
	Hepatosplenic T cell Lymphoma
	Hepatosplenic T-cell Lymphoma
	LGL*
	Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma
	NK/T-cell
	PTCL Anaplastic Large Cell Lymphoma (ALCL) ALK Negative (-)
	Primary Cutaneous Gamma/Delta T-cell Lymphoma
	T-Cell Prolymphocytic Leukemia
	T-cell prolymphocytic leukemia
	aggressive epidermotropic CD8+ **
	gamma-delta T-cell lymphoma
	hepatosplenic T Cell lymphoma
	hepatosplenic gamma-delta T cell lymphoma

*LGL (large granular lymphocytic leukemia) was miscategorized as PTCL at study entry

**CTCL with aggressive epidermotropic CD8+ was miscategorized as PTCL at study entry

C. Lugano Criteria for Response Assessments in NHL (Protocol Amendment 9 Table A4-11).

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 Nonmeasured lesions Organ enlargement New lesions Bone marrow	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment Not applicable Not applicable None No change from baseline	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 No increase consistent with progression No increase consistent with progression None Not applicable
Progressive disease Individual target nodes/nodal masses Extranodal lesions Nonmeasured lesions	Progressive metabolic disease 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 None	Progressive disease requires at least 1 of the following PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm, and Increase by > 50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions < 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (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 New or clear progression of preexisting nonmeasured lesions
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.