NCT #: NCT03372057

STATISTICAL ANALYSIS PLAN
Protocol VS-0145-225

A Multi-Center, Phase 2, Open-label, Parallel Cohort Study of Efficacy and Safety of Duvelisib in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

Protocol Version:	7.1
Type of Analysis Plan:	Final Analyses
Version:	7.0
Date:	August 7, 2023
Author:	[redacted] [redacted] [redacted] Parexel International

SPONSOR SIGNATURE PAGE

Approved by: [redacted] 30 August 30, 2023

Date

[redacted]

Secura Bio, Inc.

PAREXEL SIGNATURE PAGE

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	[redacted] Project Role: Biostatistics Lead

REVISION HISTORY

Version	Date	Brief Summary of Changes
1.0	December 18, 2018	
1.1	May 9, 2019	Update SAP after conclusion of Dose Optimization Phase and selection of optimal dose (based on the protocol v4.0)
2.0	November 7, 2019	Final Version
3.0	March 13, 2020	Add additional interim analysis for dose expansion phase.
3.1	February 4, 2021	Add Japanese subgroup analyses. Add new interim analysis. Refine definition of disease control rate. Incorporate Sponsor change from Verastem to Secura Bio.
4.0	February 25, 2021	Final Version
4.1	September 20, 2021	Update to include additional subjects added to expansion phase per protocol v7.0 and add additional interim analysis
4.2	October 15, 2021	Incorporate internal review comments
5.0	November 5, 2021	Final Version
5.1	March 29, 2022	Updates per Sponsor request to support FDA submission.
6.0	April 11, 2022	Final Version
6.1	March 31, 2023	Updates per Sponsor request to add additional analyses: - response and PFS by prognostic factors -response, PFS, DOR, and OS by major histologic subtypes - Summaries of Grade 3 or Higher SAEs, Grade 3 SAEs, Grade 4 SAEs
6.2	May 10, 2023	Add additional exploratory analyses
7.0	August 7, 2023	Final Version

TABLE OF CONTENTS

List of Abbreviations

Abbreviation	Definition
18FDG-PET	[18F] Fludeoxyglucose-positron emission tomography
AE	Adverse event
AITL	Angioimmunoblastic T-cell lymphoma
ALC	Absolute lymphocyte count
ALCL	Anaplastic large cell lymphoma
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BID	Twice daily
BV-CHP	Brentuximab Vendotin, Cyclophosphamide, Doxorubicin, Prednisone
CHOEP	Cyclophosphamide, Doxorubicin hydrochloride, Vincristine sulfate, Etoposide, Prednisone
CHOP	Cyclophosphamide, Doxorubicin hydrochloride, Vincristine sulfate, Prednisone
CR	Complete response
CSP	Clinical Study Protocol
CT	Computed tomography
CX	Cycle X
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
DX	Day X
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ICF	Informed consent form
Ig	Immunoglobulin
IRC	Independent Review Committee
ITT	Intent-to-treat
IWG	International Working Group
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI3K	Phosphoinositide-3-kinase
PO	Oral(ly)
PR	Partial response
PT	Preferred term
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma – not otherwise specified
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
US	United States
WBC	White blood cell count

1 Introduction

This statistical analysis plan (SAP) provides a detailed description of the statistical methods and analyses to be carried out in support for study VS-0145-225.

2 Study Objectives

2.1 Primary Objective

2.1.1 Dose Optimization Phase

- To determine the optimal duvelisib dose for utilization in the Expansion Phase by evaluating the ORR supported by safety, additional efficacy, and pharmacokinetics (PK) parameters as well as any other available data in the population of patients receiving the optimal dose of duvelisib for at least one cycle in patients with relapsed or refractory PTCL.

2.1.2 Expansion Phase

- To determine the efficacy of the optimal dose of duvelisib in patients with relapsed or refractory PTCL

2.2 Secondary Objectives

2.2.1 Dose Optimization Phase

- To evaluate additional efficacy parameters for duvelisib in the population of patients receiving duvelisib for at least one cycle in patients with relapsed or refractory PTCL
- To characterize the tolerability and safety of duvelisib in patients with relapsed or refractory PTCL
- To evaluate pharmacokinetics (PK) of duvelisib and if applicable, its metabolite(s)

2.2.2 Expansion Phase

- To evaluate additional efficacy parameters for duvelisib
- To characterize the tolerability and safety of duvelisib in patients with relapsed or refractory PTCL
- To evaluate PK of duvelisib and if applicable, its metabolite(s)

2.3 Exploratory Objectives

2.3.1 Dose Optimization Phase

- To evaluate pharmacodynamic and prognostic biomarkers

2.3.2 Expansion Phase

- To evaluate pharmacodynamic and prognostic biomarkers

Study Endpoints

2.4 Primary Endpoint

2.4.1 Dose Optimization Phase

Objective Response Rate (ORR, defined as complete response (CR) + partial response (PR)), as assessed by the Investigator, as determined using the Lugano criteria (Cheson et al, 2014), in the population of patients receiving the optimal dose of duvelisib for at least one cycle of study therapy.

2.4.2 Expansion Phase

ORR (CR+PR), as assessed by the Independent Review Committee (IRC), in the modified Intent-to-treat (mITT) Population, according to Lugano criteria (Cheson et al, 2014)

2.5 Secondary Endpoints

2.5.1 Dose Optimization Phase

- Duration of response (DOR), for those patients with CR or PR, defined as the time from the first documentation of response to the first documentation of progressive disease (PD), or death due to any cause
- Treatment-emergent adverse events (TEAEs) and changes in laboratory values
- Progression-free survival (PFS), defined as the time from the first study drug dose to the first documentation of PD, or death from any cause
- Disease control rate (DCR), defined as CR + PR + stable disease ≥ 8 weeks
- Overall survival (OS) and deaths
- PK parameters of duvelisib and its metabolites

2.5.2 Expansion Phase

- TEAEs and changes in laboratory values
- DOR, for those patients with CR or PR, defined as the time from the first documentation of response to the first documentation of PD, as determined by the IRC, or death due to any cause
- PFS, defined as the time from the first dose of study treatment to the first documentation of PD, as determined by the IRC, or death from any cause
- DCR, defined as CR + PR + SD ≥ 8 weeks, calculated using IRC-determined responses
- OS and deaths
- PK parameters of duvelisib and its metabolites

2.6 Exploratory Endpoints

2.6.1 Dose Optimization Phase

- Analysis of PTCL tumor pharmacodynamic markers in relation to PK, safety, and efficacy
- Analysis of PTCL tumor prognostic markers in relation to safety and efficacy
- Analysis of cytokines and non-tumor immune populations in relation to safety and efficacy
- Additional exploratory analyses identified by the Sponsor may be performed on study samples

2.6.2 Expansion Phase

- Analysis of duration of complete response

- Subgroup analysis of select efficacy and safety endpoints.
- Analysis of PTCL tumor pharmacodynamic markers in relation to PK, safety, and efficacy
- Analysis of PTCL tumor prognostic markers in relation to safety and efficacy
- Analysis of cytokines and non-tumor immune populations in relation to safety and efficacy
- Additional exploratory analyses identified by the Sponsor may be performed on study samples

3 Study design

3.1 Overview

This is a multi-center, parallel cohort, open-label, Phase 2 study of duvelisib, an oral dual inhibitor of PI3K-δ, γ, in patients with relapsed/refractory PTCL.

The study has 2 phases, a Dose Optimization Phase and an Expansion Phase.

Regardless of study phase, all patients will undergo screening assessments up to 30 days before the first study drug dose (Cycle 1, Day 1 [C1D1]). Patients meeting all of the entrance criteria, based on Screening assessments, will be enrolled in the study and receive the first study drug dose on C1D1. Thereafter, patients will attend study center visits as per the applicable Phase Schedule of Events (Dose Optimization: Study Protocol Table 1, Expansion Phase: Study Protocol Table 2). At screening, disease will be measured using 18F-fluorodeoxyglucose-positron emission tomography (18FDG-PET)-computed tomography (CT) scanning (PET-CT) (CT images along with PET should be diagnostic with contrast unless contraindicated), Where PET-CT is not feasible, CT with contrast or magnetic resonance imaging (MRI) may be used after discussion with the Medical Monitor. Subsequently, for FDG-avid PTCL, PET-CT will be used to assess disease status and for FDG-non-avid PTCL, CT with contrast or MRI will be appropriate substitutes. The modality chosen to evaluate response in each individual patient should be the same throughout the duration of the study. For the purposes of patient management during the conduct of the study, the Investigator's assessment of disease response will be used. Images also will be centrally stored, and disease response will be determined by an IRC for futility and at the end of the study.

3.1.1 Dose Optimization Phase

The Dose Optimization Phase will be conducted at up to approximately 15 centers in the US.

In the Dose Optimization Phase, patients will be randomly assigned at a 1:1 ratio to 1 of 2 study cohorts, as follows:

- Cohort 1: Duvelisib orally (PO) twice daily (BID) at a starting dose of 25 mg, with potential escalation on a per-patient basis to 50 mg BID and then 75 mg BID, based on the patient's response to and tolerance of therapy, in 28-day cycles.

- Cohort 2: Duvelisib 75 mg PO BID, administered in 28-day cycles.

Approximately 10 patients each will be enrolled in Cohorts 1 and 2. Patients in the Dose Optimization Phase who discontinue before receiving at least 1 cycle of study drug may be replaced. Enrollment into the Dose Optimization Phase may continue until the initiation of the Expansion Phase.

For both cohorts, dose modification criteria for duvelisib will be applied if the starting dose or a subsequent dose of Duvelisib is deemed intolerable (see Section 8.4.2 of the Clinical Study Protocol (CSP)). Dose Optimization Phase patients will complete treatment as defined for their cohort.

Cohort 1

All patients will receive duvelisib at a starting dose of 25 mg PO BID (Level 1), with potential sequential escalation to 50 mg PO BID (Level 2), and then to 75 mg PO BID (Level 3). Intrapatient dosing decisions will occur as follows:

- After completion of Cycle 1 and every 2 cycles thereafter:
    - Patients with CR or PR will have their duvelisib dose maintained at the current dose level.
    - Patients with stable disease (SD) who are, in the Investigator's opinion, tolerating and otherwise suitable to continue receiving therapy, will have the duvelisib dose increased to the next level until the next response assessment or development of PD or intolerance, as determined by the Investigator.
- Patients with PD who are not, in the Investigator's opinion, tolerating therapy or otherwise not suitable to continue receiving therapy will discontinue duvelisib.

In no case will the duvelisib dose be increased to a level > 75 mg BID (total daily dose 150 mg).

All patients in Cohort 1 will receive duvelisib until development of PD or unacceptable toxicity, as determined by the Investigator.

Cohort 2

All patients in Cohort 2 will receive duvelisib 75 mg PO BID in 28-day cycles until development of PD or unacceptable toxicity, as determined by the Investigator.

3.1.2 Expansion Phase

The Expansion Phase will be conducted at approximately 40-50 centers globally.

At the conclusion of the Dose Optimization Phase, efficacy, PK, and safety data as well as any other available data will be taken into consideration to recommend the optimal dose for the Expansion Phase. In addition to recommending an optimal dose, the Expansion Phase may also involve modifications of the study patient population, other aspects of entry criteria, and the inclusion of patients from geographic regions outside the United States (US); any such changes will be documented in an amendment to the protocol. Patients will have disease assessment after Cycle 2 and every 2 cycles thereafter until the follow-up stage is reached and assessment will occur according to Table 4 of the CSP.

With protocol amendment 7.0, 20-30 additional patients will be enrolled in the Expansion Phase for a total of up to 130 patients.

Expansion Phase Dose Selection:

As of January 2, 2019, 20 patients met the criteria for the Dose Optimization efficacy population and available data as of February 11, 2019, was reviewed. A dosage of 75 mg BID for the first 2 cycles, followed by a mandatory reduction to 25 mg BID thereafter for those patients with CR, PR or SD, will be used for the Expansion Phase. The dose may be re-escalated to 75 mg BID based on response assessment and safety (see CSP Sections 1.3 and 8.1.2).

3.2 Randomization

In the Dose Optimization Phase only, patients will be randomly assigned on C1D1 to either Cohort 1 or 2 on a 1:1 basis via a computer-generated randomization scheme. No stratification methodology will be employed in this study.

3.3 Sample Size Considerations

Approximately 20 patients will be enrolled in the Dose Optimization Phase, with approximately 10 evaluable patients per cohort. However, enrollment may discontinue in either cohort if no CR/PR, as assessed by the Investigator, is noted in the first 5 evaluable patients per cohort. This stopping rule is based on the first stage decision rule of a Simon 2-stage design, with assumptions of a hypothesized ORR of 50% and a null rate of 15% with a one-sided alpha of 0.05 and a power of 85%.

Patients in the Dose Optimization Phase who discontinue before receiving at least 1 cycle of study drug may be replaced.

In the Expansion Phase, the target enrollment is approximately 100 patients with a centrally confirmed diagnosis of PTCL. It is anticipated up to 5% of patients may have a diagnosis that is not confirmed upon central pathology review. One-hundred patients will provide 99.2% power to distinguish between a null ORR of 20% and an alternative ORR of 40% with a two-sided alpha of 0.05. Further, with 100 patients treated at the optimal duvelisib dose, the obtained ORR will have 95% confidence bounds of no greater than ± 10% when the normal approximation method is employed (assumes 50% ORR). If the observed ORR is greater or less than 50%, the confidence bounds will be less than ± 10%. These bounds around the obtained ORR are thought to adequately characterize the effect of the optimal dose of duvelisib in this PTCL population.

With protocol amendment 7.0, 20-30 additional patients will be enrolled in the expansion phase. Assuming a total of 120 or 130 patients the power to distinguish between a null hypothesis of ORR of 20% and an alternative ORR of 40% will be 99.4% or 99.6%, respectively.

The primary analysis for the Expansion Phase will be performed once approximately 100 patients with a centrally confirmed diagnosis of PTCL have been enrolled and evaluated for the primary endpoint. In the event that enrollment in the expansion phase exceeds 110% of the planned sample size, a sensitivity analysis will be performed on the first 100 patients enrolled in the Expansion Phase.

The final analysis for the Expansion phase will be performed once all patients with a centrally confirmed diagnosis of PTCL have been enrolled and evaluated for the primary endpoint. The total number of patients (up to 130) will be determined by the Sponsor. An important driver of the final sample size may be the number of additional patients needed to add an additional 8-10 patients having PTCL subtype of either ALCL or NK cell.

3.4 Blinding

No blinding of treatment assignment will be used in this study.

3.5 Interim Analysis and Data Review

As noted in Section 3.3, during the dose optimization phase, the ORR for each dose optimization cohort will be reviewed when 5 patients are determined to be evaluable. If no response of CR or PR has been observed in the cohort then enrolment in that cohort will be discontinued. Evaluation of response in this analysis will be based on Investigator assessments.

In addition, at the conclusion of the Dose Optimization Phase, all available data will be reviewed and an optimal dose for the Expansion Phase will be selected. In addition to recommending an optimal dose, the Expansion Phase may also involve modifications of the study patient population, other aspects of entry criteria, and the inclusion of patients from geographic regions outside the US; any such changes will be documented in an amendment to the protocol. The Sponsor study team, in collaboration with the Investigators, will make the determination of duvelisib dose for the Expansion Phase of the study based on the totality of available safety and activity data. This evaluation does not constitute an interim analysis.

During the expansion phase, two assessments of ORR will be conducted. The first will be a preliminary assessment of ORR after approximately 15 subjects have had an initial assessment of response by the investigator. During this assessment, the data from the expansion phase will be reviewed in the context of data from the dose optimization phase.

The second assessment will occur after 40 patients have been followed for a minimum of 4 months from the last patient's first dose and assessed for response by the IRC. At that time, enrollment in the Expansion Phase may be held if ORR is less than 20%. The efficacy data (including durability of response) will be reviewed in combination with safety and PK and upon review, the study may be fully stopped for futility.

- Additional interim analyses will be used for planning purposes, FDA submission and discussion and possible publication of early efficacy and safety results. The final analysis of the study will be completed and submitted to health authorities and published as appropriate. The approximate timing of these interim analyses are when: At least 75 of expansion phase patients have been followed for a minimum of 6 months from the last patient's first dose and assessed for response by the IRC.
- All patients enrolled prior to protocol v7.0 (101 patients) who have been followed for a minimum of 6 months from the last patient's first -scheduled response assessment (*i.e.,* 8 months from their first dose) and who have response assessed by the IRC.

3.6 Analysis Sets

3.6.1 Dose Optimization Efficacy Set

Dose Optimization Efficacy Set will consist of all patients who 1) receive at least one dose of study drug and 2) complete at least one cycle of treatment and 3) have at least one scan to assess disease response after completion of one cycle of treatment.

Efficacy analyses for the dose optimization phase will be performed using the Dose Optimization Efficacy Set for all primary and secondary efficacy analyses using the response determined by the Investigator. The IRC's determination of disease response will be used in supportive efficacy analyses.

3.6.2 Modified Intent-to-treat (mITT) Analysis Set

The mITT Population will consist of patients who receive at least one dose of study drug.

Efficacy analyses for the dose expansion phase will be performed using the mITT Analysis Set for all primary and secondary efficacy analyses using the response determined by IRC.

3.6.3 Safety Analysis Set

The Safety Population consists of all patients receiving at least 1 dose of duvelisib.

Safety analyses will be performed using the Safety Analysis Set.

4 General Statistical Methods and Data Handling

4.1 General Methods

Summary statistics will be presented by treatment group, unless stated otherwise.

Unless otherwise specified, descriptive statistics for continuous data will include the number of subjects with data to be summarized (n), mean, standard deviation, 25% quartile, median, 75% quartile, and minimum and maximum. The same number of decimal places as in the raw data will be presented when reporting the minimum and maximum, one more decimal place than the raw data will be presented when reporting mean and median, and 2 more decimal places than the raw data will be presented when reporting standard deviation.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects in the treatment group will be used as the denominator for percent calculations, unless stated otherwise. All percentages will be presented with one decimal, unless otherwise specified. Percentages equal to 100 will be presented as 100, and percentages will not be presented for zero frequencies.

Descriptive statistics associated with time-to-event analyses will include the number of events, the number of subjects censored, 25% quartile, median, 75% quartile, and 95% confidence interval for median. These statistics will be presented for all time-to-event analyses, unless stated otherwise.

Listings will be provided for selected endpoints.

4.2 Treatment-emergent Adverse Event (TEAE) Definition

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product. This includes an exacerbation of pre-existing conditions or events, concurrent illnesses, drug interaction, or the significant worsening of the indication under investigation. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Symptoms of the disease under study / lack of efficacy / disease progression should not be classified as an AE as long as they are within the normal day-to-day fluctuation or expected progression of the disease.

The onset date of an AE will be compared to the first dose date and the last dose date plus 30 days (inclusive) to determine whether the AE is treatment-emergent or not. Adverse events occurring on the first dose date will be considered treatment emergent unless otherwise indicated on the eCRF.

4.2.1 Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence at any dose (including after the Informed Consent Form (ICF) is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not immediately life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such 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.

4.3 Handling of Missing Data

4.3.1 Handling of Missing Dates/Months/Years for Determination of TEAEs

Adverse events with incomplete onset dates will be handled as follows for the purpose of determining treatment emergence according to the definition above.

- If the start/end date of an AE is partially missing, the date will be compared as accurately as possible with the first dose of study drug and the date of last dose of study drug plus 30 days. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not start or worsen during the treatment-emergent period.

- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before first dose of study drug.

The original partial or missing date will be displayed in listings of AEs.

4.3.2 Handling of Missing Dates/Months/Years for Concomitant Medications

Prior or concomitant medications with incomplete start dates will be handled as follows for the purpose of determining whether a non-study medication is a concomitant medication:

- If the start/stop date of a medication is partially missing, the date will be compared as accurately as possible with the first dose date of study drug and the last dose date of study drug plus 30 days. The medication will be assumed to be concomitant if it cannot be definitively shown that the stop date is before first dose date of study drug, or the start date is more than 30 days after the last dose date of study drug.
- If the start/stop dates are completely missing, a medication will be considered concomitant.

4.3.3 Handling of Missing Dates for Disease History

For the purpose of calculating the duration from initial diagnosis, partial/missing dates for diagnosis will be imputed as follows:

- If both day and month are missing and the year is prior to the year of screening, the imputed date will be 01 July
- If both day and month are missing and year is the same as the year of screening, the imputed date will be the middle point between 01 January of the year and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- If day is missing and the month and year are prior to the month and year of screening, the imputed date will be the 15th day of the month.
- If day is missing and the month and year are the same as the month and year of screening, the imputed date will be the middle point between the first day of the month and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- No imputation will be performed if the year is missing.

4.4 Multiple Comparisons/Multiplicity Adjustment

No adjustment for multiple comparisons will be performed for this study.

4.5 Subgroups

4.5.1 Subgroups based on baseline demographics and disease characteristics

The following subgroups may be examined for key efficacy and safety endpoints.

- Age group (< 65 years vs. ≥ 65 years)
- Gender (Male, Female)
- Race (Asian, Black or African America, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Geographic Region (US, Europe, Japan)
- Baseline BMI (kg/m^2 ; < median, ≥ median)
- Baseline ECOG performance status (0, 1, 2)
- Time since initial diagnosis (< median, ≥ median)
- Histopathological diagnosis*
- Time since most recent relapse/refractory diagnosis (months; < median, ≥median)
- Initial stage (I/II, III, IV)
- Baseline stage (I/II, III, IV)
- Initial Ann Arbor stage (A, B, E, S)
- Baseline Ann Arbor stage (A, B, E, S)
- Number of prior regimens (1, 2, 3 or more)
- Time since most recent treatment (weeks; < median, ≥ median)
- Best response to most recent prior treatment (CR, PR, SD, PD)
- Prior radiotherapy (Yes, No)
- Prior Surgery (Yes, No)
- Prior CHOP (Yes, No)
- Prior CHOEP (Yes, No)
- Prior CHOP or CHOEP (Yes, No)
- Prior Salvage Chemotherapy after CHOP or CHOEP (Yes, No)

- Prior BV-CHP (Yes, No)
- Prior stem cell therapy (Yes, No)
- By major histology (PTCL-NOS, AITL, ALCL, Other)
- Non-AITL vs. AITL
- Non-ALCL vs. ALCL

*Categories for histopathological diagnosis will be based on the data observed and will include distinct categories for each common type (major histologic subtypes), and an "Other" category to combine types with less than 3 patients (minor histologic subtypes).

Prior CHOP will be defined as patients who received cyclophosphamide, doxorubicin, vincristine, and prednisone in a single prior regimen that does not include etoposide. Prior CHOEP will be defined as patients who received cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone in a single prior regimen. Prior salvage chemotherapy after CHOP or CHOEP will be defined as patients who had any other chemotherapy regimen following a regimen of CHOP or CHOEP. Prior BV-CHP is defined as patients who received brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone in a single regimen.

4.5.2 Prognostic factors

A subgroup analysis for the following prognostic factors and each of their components (where applicable) will be performed for key efficacy endpoints.

- All major histologic subtypes except for anaplastic large-cell lymphoma (ALCL)
- All major histologic subtypes except for Angioimmunoblastic T-cell lymphoma (AITL)
- Baseline international prognostic index (IPI) score and each component
- Received a stem cell transplant post baseline (yes, no)

IPI score is derived by assigning one point for each of the 5 components. A score of 0-1 is considered 'Low', a score of 2-3 is considered 'Intermediate', and a score of 4-5 is considered 'High'. Components:

- Age > 60 years
- Baseline stage III or IV disease
- Baseline ECOG score ≥ 2
- Baseline lactate dehydrogenase > ULN
- 2 or more extranodal lesions (target or non-target)

.

4.6 Visit Windows

Treatment visits, cycles, and days are pre-defined for this study and are pre-specified on the CRF. In the presentation of study data using Study Day and Cycle Day, the following derivations will be used:

- Day 1 of Study = Date of first dose for a patient
- Study Day = Date – Date of first dose + 1, if Date is on or after Date of first dose
  or Study Day = Date – Date of first dose, if Date is before Date of first dose

- Day 1 of Cycle = Date of cycle start, as reported on eCRF (per protocol, Day 1 of Cycle 1 should be Day 1 of Study)
- Cycle Day = Date – Date of cycle start in current cycle + 1

4.7 Baseline Values

Unless otherwise specified, the baseline value is defined as the most recent value prior to first study drug administration.

4.8 Computing and Coding Standards

Computing, coding, and grading standards are provided in the following table.

Table 1: Computing, coding and grading standards	
Table, listing, and figure production	SAS Version 9.2 or higher
Coding	
Adverse Events	Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher
Medical Histories	MedDRA Version 20.1 or higher
Prior and Concomitant Medications	WHODrug Version Mar. 2013 or higher
Prior and post Systemic Therapy	WHODrug Version Mar. 2013 or higher
Grading	
AEs	Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
Laboratory Results	CTCAE Version 5.0

5 Statistical Analyses

5.1 Study Subjects

5.1.1 Disposition of Subjects

The number and percentage of patients in each analysis set will be provided. This includes the Safety Analysis Set, mITT and the Dose Optimization Efficacy Set. The percentage will be based on the number of patients in the Safety Analysis Set. Disposition of patients will be summarized for the Safety Analysis Set. The number and percentage of enrolled patients, treated patients, patients entered follow-up, patients who completed the study, and patients who discontinued the study and reasons for discontinuation will be summarized. Disposition of patients will be summarized for the overall population as well as by different cohorts and by phase.

Time to treatment discontinuation will be summarized for subjects who have discontinued treatment at time of data cut-off. Follow-up time (from 1st dose to last contact on or prior to data cut-off) will be descriptively summarized. For responders, follow-up time from first response to last contact on or prior to data cut-off will also be summarized.

5.1.2 Protocol Deviations

Protocol deviations will be categorized as major or minor prior to data release for the futility analysis and final analysis of the primary endpoint. A summary table of the major protocol deviations will be provided by cohort and by phases for the mITT Analysis Set. A listing of major protocol deviations will be provided.

5.1.3 Demographic and Other Baseline Characteristics

Demographic variables and other baseline characteristics will be summarized by phase and treatment based on Safety Analysis Set. The variables to be summarized will include (but will not be limited to):

- Age (continuous variable)
- Age group (< 65 vs. ≥ 65)
- Gender
- Race
- Ethnicity
- Geographic Region (US, Europe, Japan)
- Body mass index (BMI), calculated as weight (kg) / (height (m))^2
- ECOG performance status

5.1.4 Baseline Disease Characteristics

Baseline PTCL characteristics will be summarized by phase and treatment based on Safety Analysis Set. The variables to be summarized will include (but will not be limited to):

- Time since initial diagnosis
- Histopathological diagnosis
- Time since most recent relapse/refractory diagnosis
- Initial stage and Ann Arbor staging
- Current stage and Ann Arbor staging
- Prior anticancer therapy, prior radiotherapy, and prior surgery
    - Number of regimens - continuous and categorical (1, 2, 3+)
    - Time since most recent treatment
    - Best response to any prior treatment
    - Best response to most recent prior treatment
    - Duration of response to most recent prior treatment
    - Prior CHOP (Yes, No)
    - Prior CHOEP (Yes, No)
    - Prior CHOP or CHOEP (Yes, No)
    - Prior Salvage Chemotherapy after CHOP or CHOEP (Yes, No)
    - Prior BV-CHP (Yes, No)
    - Prior stem cell therapy (Yes, No)

5.1.5 Medical History

Medical history will be summarized by phase and treatment based on the Safety Analysis Set.

Medical history will be summarized by system organ class (SOC) and preferred term (PT) using the number and percentage of patients who had at least one occurrence of an SOC or PT. The summary will be sorted alphabetically by SOC and by decreasing frequency of PT within an SOC.

5.1.6 Prior and Concomitant Medications

Medications will be considered as prior if they stopped before the date of first dose of study drug.

Medications will be considered concomitant if they were taken at any time between the first dose of study drug and 30 days after the last dose of study drug, inclusive. If the start date or end date of a medication is completely or partially missing refer to Section 4.3.2 for the algorithm to determine whether a medication is concomitant.

Prior medications and concomitant medications will be summarized separately. Both summaries will be based on the Safety Analysis Set. Prior anti-cancer systemic therapies will be summarized separately from other prior medications.

Medications will be summarized by phase and treatment by anatomical therapeutic chemical (ATC) level 1, ATC level 2, and preferred drug name for each cohort. The summary will be sorted by decreasing frequency in ATC level 1, ATC level 2 and preferred drug name. A patient taking the same drug multiple times will be counted once.

A listing will be provided for all non-study medications taken on the study. An identifier will be provided to show if a medication is prior to concomitant. Medications that started more than 30 days after the last dose of study drug will be identified as post-treatment.

Additional groupings of medications will be defined to identify medications administered to treat adverse events specific to the duvelisib risk profile.

5.1.7 Exposure to Study Drug

Extent of exposure will be summarized by phase and treatment based on the Safety Analysis Set.

Extent of exposure will be summarized for the following variables by cycle and overall:

- Duration (weeks): (date of last dose – date of first dose + 1) divided by 7.
- Treatment duration categories (≤56 days, 57 – 112 days, > 112 days)
- Number of cycles started (continuous and categorical)
- Cumulative dose received (mg) (continuous and categorical by quartiles)
- Cumulative dose received (mg) during Cycles 1 and 2 (continuous and categorical by quartiles)
- Dose Intensity (mg/day) defined as total actual dose divided by duration in days
- Relative dose intensity, defined as 100% x (total dose received)/(planned cumulative dose for the duration of treatment)
- Average daily dose received (mg)
- Number and percentage of patients within Dose Optimization Cohort 1 with dose escalations to 50mg BID and 75mg BID
- Number and percentage of patients with a dose reduction
- Number and percentage of patients with a dose hold
- Number and percentage of patients for whom study drug was discontinued

Cumulative dose quartiles will be based on doses for all patients in the safety analysis set with all treatment groups combined.

For relative dose intensity, planned dose is defined as follows:

- Dose Optimization Cohort 1: 25 mg × 2 × total days treated at starting dose. For subjects whose assigned dose escalated due to SD at the end of Cycles 1 and 3 as described in the CSP, raise the planned dose accordingly.
- Dose Optimization Cohort 2: 75 mg × 2 × total days treated

- Expansion Phase: 75 mg × 2 × (28 × 2) + 25 mg × 2 × (total days treated – (28×2)) if patient receives > 2 cycles of treatment *or* 75 mg × 2 × total days treated if patient received < 2 cycles of treatment.

Where total days treated = last dose date – first dose date + 1.

A by-patient listing will be presented for exposure to study drug. A separate listing of dose modifications will be provided for patients who received at least one dose modification.

5.2 Efficacy Analyses

For the Dose Optimization Phase, all primary and secondary efficacy analyses will be performed using the Dose Optimization Efficacy Set and will be based on the Investigator's determination of response, with the IRC's determination of response used for supportive efficacy analyses. Analysis of the Expansion Phase primary and secondary efficacy analyses will be performed using the mITT Analysis Set and will be based on the IRC's determination of response, with the Investigator's determination of response used for supportive efficacy analyses. Response will not require confirmation by a second assessment.

Listings of efficacy endpoints will be provided. The listing of best overall response (including unknown response) will include histological type, reason for treatment discontinuation, flag for death, and time to death.

5.2.1 Analyses of Primary Endpoint

5.2.1.1 Primary Analysis of ORR/BOR

ORR and BOR as determined by both the IRC and the Investigator will be presented along with 2-sided confidence intervals using normal approximation.

Swimmer's plots will be produced with time on study as the x-axis and patient ID along the y-axis. Different symbols representing the study day of each IRC response (CR, PR, SD, PD, NED), end of treatment reason (PD, AE, death, transplant, other), and end of study reason (death, other) will be plotted for each patient. Patients will be grouped by best overall response.

5.2.1.2 Subgroup Analysis of ORR/BOR

Subgroup analysis of ORR by subject demographics and baseline disease characteristics will be tabulated using response determined by the IRC in the mITT Analysis Set. BOR will be analyzed by select subgroups. Potential subgroups to be included are described in Section 4.5.

5.2.1.3 ORR/BOR by prognostic factors

The primary analysis will be repeated by the prognostic factors described in section 4.5.2. A forest plot will be presented for the expansion phase and for all patients combined plotting ORR with 95% CI for each prognostic factor and component.

5.2.2 Analyses of Secondary and Exploratory Efficacy Endpoints

5.2.2.1 Duration of Response

Duration of response will be analyzed both for patients with ORR (CR or PR) and for patients with CR.

- Main DOR Analysis: DOR will only be calculated for those patients with a CR or PR from time to first response to PD or death (if death occurs prior to PD). Patients who withdraw from the study for any reason prior to PD and patients who have ongoing response at the time of the data cut will be censored at the date of their last response assessment.
- Duration of complete response (DOCR): DOCR is calculated from the time of first CR and only includes patients who had at least one CR response. It is otherwise defined the same as the Main DOR endpoint.

Estimates of the 25th percentile, median, and 75th percentiles will be for each of these DOR endpoints will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median DOR will be provided by using the Brookmeyer-Crowley method. Kaplan-Meier plots will be provided.

In addition, the number and percent of patients with duration of response of at least 3 months, 6 months and 12 months will be tabulated.

A summary of time to first response will also be presented in patients who achieved CR or PR and in patients who achieved CR.

5.2.2.2 Disease Control Rate

The proportion of patients demonstrating DCR (defined as patients with best overall response of CR or PR or with best overall response of SD sustained for at least 8 weeks) will also be presented along with 2-sided confidence intervals.

5.2.2.3 Analysis of PFS

For the PFS analyses, censoring of PFS will be performed as detailed in Table 2. Note that progression may be documented based on scheduled or unscheduled disease status assessment, and that unscheduled disease status assessments will be included in calculating the gap between adequate disease status assessments.

PFS will be estimated for each cohort using the Kaplan-Meier method. PFS will be plotted by using the Kaplan-Meier method. Number of patients with events, type of events (progression or death), number of patients censored, number of patients for each reason of censoring, Kaplan-Meier estimates and 95% confidence intervals for the 25th percentile, median, and 75th percentile for PFS will be presented. A 2-sided 95% confidence interval for median PFS will be provided by using the Brookmeyer-Crowley method. Probabilities of remaining alive and progression free at selected time points may also be presented.

PFS analysis will be repeated for the subset of enrolled Japanese patients and for each of the prognostic factors described in section 4.5.2

Table 2: Primary PFS Censoring/Event Rule

Situation	Date of Event or Censoring	Outcome
No adequate baseline disease status assessment	Date of randomization + 1 day	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first scheduled post-baseline assessment	Date of randomization + 1 day	Censored

No documented progression or death	Date of last adequate disease status assessment	Censored
Documented progression with ≤1 missing scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of unequivocal progression	Event
Death before progression being documented with ≤1 missing scheduled disease status assessment before death	Date of death	Event
Documented progression or death following a gap between adequate disease status assessments equivalent to 2 missed visits	Date of last adequate disease status assessment before the gap	Censored
New anticancer treatment or procedure started before documented progression or death.	Date of last adequate disease status assessment prior to start of new anticancer therapy	Censored

Note: Disease status assessment includes radiologic documentation (CT, PET/CT, MRI scans) (chest, abdomen and pelvis, others as clinically indicated), bone marrow biopsy/aspirate (may not be required of all patients at all scheduled disease status assessments), and focused physical examination (disease related symptoms, liver and spleen assessment). An adequate baseline disease assessment is any assessment with measurable target lesions from scans. An adequate post-baseline disease status assessment is any disease status assessment for which a disease status of CR, PR, SD or PD is arrived per revised International Working Group (IWG) response criteria for malignant lymphoma[2].

5.2.2.4 Overall Survival

OS will be assessed using Kaplan-Meier methods from time of first treatment to death using the same methods described for PFS. Patients without documented death will be censored at last alive date. OS analysis will be repeated for the subset of enrolled Japanese patients.

5.2.2.5 Sum of Target Lesions

The best (minimum) percent change from baseline in sum of all target lesions will be summarized (mean, standard deviation, minimum, and maximum) for both IRC and investigator assessment of target lesions overall and by best overall response. A waterfall plot will be produced for each phase/treatment. Each subject's best percent change will be classified by best overall response (CR, PR, SD, PD).

5.2.3 Exploratory Efficacy Analyses

Logistic regression (ORR) and Cox regression models (time to event endpoints) may be used to explore the impact of prognostic factors and other important baseline characteristics on response. For each of these potential explanatory variables a simple model with each variable as the sole predictor will be run. In addition, models with multiple potential explanatory variables may be fit in the same model and model selection techniques used to examine which combination of variables best predict response (logistic regression models) or best describe the hazard function (Cox models). These exploratory analyses may or may not be presented formally. Further details on these analyses may be outlined in a separate analysis plan, and results may be summarized in a separate report.

5.3 Safety Analyses

5.3.1 Adverse Events

Adverse events will be coded using MedDRA Version 20.1 or higher. The severity grade of the TEAE will be assessed by the Investigator according to the NCI-CTCAE Version 5. If a TEAE is not included in the NCI-CTCAE definitions, the severity grade of the TEAE will be assessed by the Investigator according to the study protocols.

TEAEs will be summarized by phase and treatment by MedDRA system organ class (SOC) and preferred term (PT), or PT only. For summary tables by SOC and PT, SOC will be sorted alphabetically, and PT will be sorted by decreasing frequency within each SOC. For summary tables by PT only, PT will be sorted by decreasing frequency.

If multiple TEAEs of the same PT occur within a patient, only the maximum grade observed for this PT will be used in summary of TEAEs by grade; the patient will be counted only once per SOC and PT.

An overview TEAE summary table will be provided including the number of patients with AEs in selected categories. In addition, TEAEs will be summarized for the following categories, and will be tabulated by SOC and PT:

- TEAEs (All Grades, All Causalities)
- Treatment-related TEAEs (All Grades)
- TEAEs by maximum grade (All Causalities)
- Treatment-related TEAEs by maximum grade
- Grade 3 or higher TEAEs (All Causalities)
- Grade 3 or higher treatment-related TEAEs
- Treatment-emergent SAEs (All Causalities)
- Grade 3 or higher SAEs (All Causalities)
- Grade 3 SAEs (All Causalities)
- Grade 4 SAEs (All Causalities)
- Treatment-related treatment-emergent SAEs
- TEAEs resulting in discontinuation of study drug (All Causalities)
- TEAEs resulting in dose hold (All Causalities)
- TEAEs resulting in dose reduction for duvelisib (All Causalities)
- TEAEs resulting in any modification to study drug administration (All Causalities); defined as discontinuation, reduction, and/or dose hold
- TEAEs resulting in death (All Causalities)
- Treatment-related TEAEs resulting in death
- TEAEs by PT (All Grades, All Causalities)
- Treatment-related TEAEs by PT (All Grades)
- Grade 3 or higher TEAEs by PT (All Causalities)
- Treatment-emergent SAEs by PT (All Causalities)
- Treatment-related treatment-emergent SAEs by PT

Three tables summarized by SOC only will be provided, sorted by descending frequency:

- All TEAEs
- All SAEs
- All TEAEs leading to treatment discontinuation.

A by-patient listing of the following AE categories will be presented.

- All AEs (TEAEs will be flagged)
- All SAEs (TEAEs will be flagged)
- TEAEs resulting in dose hold
- TEAEs resulting in dose reduction
- TEAEs resulting in discontinuation of study drug
- TEAEs resulting in death

5.3.1.1 Other Adverse Events of Interest

Selected MedDRA PTs will be combined to create grouped PTs or categories to further characterize risks associated with duvelisib. The following risks will be summarized:

Grouped Term	**Preferred Terms**
Diarrhea	Diarrhoea, Diarrhoea hemorrhagic, Defecation urgency
Colitis	Colitis, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic, Colitis microscopic, Necrotising colitis, Colitis ulcerative
Pneumonia	Pneumonia, any PT containing the word/string "pneumonia" except for "Pneumonia aspiration", Atypical pneumonia, Atypical mycobacterial pneumonia, Bronchopneumonia, Bronchopulmonary aspergillosis
Pneumonitis	Pneumonitis, Interstitial lung disease, lung infiltration, acute interstitial pneumonitis
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased, Hypertransaminasaemia, Hepatic enzyme increased, Acute hepatic failure, Drug-induced liver injury, Hepatic failure, Hepatocellular injury, Hepatotoxicity
Cutaneous reactions	Dermatitis, Dermatitis allergic, Dermatitis bullous, Dermatitis exfoliative, Dermatitis psoriasiform, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalised erythema, Exfoliative rash, Rash, Rash generalised, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash papular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Perivascular dermatitis, Skin reaction, skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis
Neutropenia	Neutropenia, Neutrophil count decreased

The specific PTs that will be combined for each risk will be defined in the analysis dataset programming specifications.
For each risk, PTs will be summarized at the grouped PT and individual PT (and grouped SOC if applicable), at the patient level:

- TEAEs (All Grades, All Causalities)
- Treatment-related TEAEs (All Grades)
- Grade 1 or 2 only TEAEs (All Causalities)

- Grade 3 or higher TEAEs (All Causalities)
- Grade 4 TEAEs (All Causalities)
- TEAEs resulting in death (All Causalities)
- Treatment-emergent SAEs (All Causalities)
- Treatment-related treatment-emergent SAEs
- TEAEs resulting in dose hold (overall and by resolution)
- TEAEs resulting in dose reductions (overall and by resolution)
- TEAEs resulting in dose hold or reductions (overall and by resolution)
- TEAEs resulting in discontinuation of study drug (overall and by resolution)
- Time to initial onset (defined as AE start date – first dose date +1)
- For all infections only a summary broken out by MedDRA High Level Terms (HLT) and High Level Group Terms (HLGT)
- TEAEs by time on treatment (up to 56 days, 57 through 112 days, > 112 days)

Only patients who entered the treatment period will be considered in summaries by treatment period (*i.e.,* if a patient withdrew from treatment between days 57 and 112 they would be included in the up to 56 days summary and in the 57 through 112 days summary, but not in the > 112 days summary).

In addition, the following summaries will be created for each grouped PT within each grouped SOC, at the event level:

- Duration of AE
- Time to Onset of AE

In addition, use of specific concomitant medications to treat each of the risks will be summarized. Concomitant medications can be associated with specific TEAEs in the clinical database, and for each adverse event of interest all medications associated with any preferred term in the group of terms will be summarized.

5.3.1.2 Adverse Event Subgroup Analysis

Summaries of TEAEs and AESI by SOC and PT may be repeated for select subgroups including: sex, age group (<65 years, ≥65years), race, geographic region, cumulative dose quartiles, cumulative dose quartiles in cycles 1 and 2, and number of prior regimens (1,2, 3+). Cumulative dose quartiles will be based on doses for all patients in the safety analysis set with all treatment groups combined.

5.3.2 Laboratory Data

Laboratory tests will be reported separately for hematology, blood chemistry and serum quantitative immunoglobulins (Ig).

For the purposes of presentation in both tables and listings, the following laboratory test results will be converted to the International System of Units (SI) before presentation: sodium, potassium, chloride, bicarbonate (or CO_2), albumin, total protein, creatinine, uric acid, calcium, phosphorus, magnesium, glucose, total and direct bilirubin, alkaline phosphatase, red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell count (WBC) with 5-part differential performed manually or by flow cytometry (lymphocytes, neutrophils, monocytes, basophils, and eosinophils), amylase, lipase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), IgA, IgM and IgG. Laboratory tests will be graded according to CTCAE Version 5.0.

If a laboratory test value is reported using a non-numeric qualifier (e.g., less than [<] a certain value or greater than [>] a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

For continuous laboratory results, descriptive statistics will be provided by visit for observed value and change from baseline. Plots of mean observed value over time will be produced for continuous laboratory test results.

For laboratory tests graded by CTCAE, the following summary tables will be created by treatment arm:

- Summary of worst post-baseline value on treatment, regardless of baseline value according to the following categories:
    - Any grade
    - Grade 1-2
    - Grade 3-4
    - Grade 3
    - Grade 4
- Summary of worst post-baseline value on treatment that represents a worsening in grade from baseline (shift table) according to the following categories:
    - Any grade
    - Grade 1-2
    - Grade 3-4
    - Grade 3
    - Grade 4

In addition, laboratory tests with Grade 3 or 4 laboratory values will be presented in a separate patient listing.

Laboratory tests with bi-directional grades (e.g., hyperglycemia and hypoglycemia) will be presented separately for each direction within each by grade summary table.

For laboratory tests not graded by CTCAE, the following summary tables will be created by treatment arm:

- Summary of worst post-baseline value on treatment, regardless of baseline value according to the following categories:
    - Low (less than lower limit of normal)
    - Normal (greater than or equal to lower limit of normal and less than or equal to upper limit of normal)
    - High (greater than upper limit of normal)
- Summary of worst post-baseline value on treatment that represents a worsening from baseline (shift table) according to the following categories:
    - Low (less than lower limit of normal)
    - Normal (greater than or equal to lower limit of normal and less than or equal to upper limit of normal)
    - High (greater than upper limit of normal)

Patients with more than one post-baseline abnormality will be counted once for each type of abnormality (low, high). Only patients with no low or high abnormalities reported will be classified as normal.

5.3.3 Vital Signs

The actual values of vital sign parameters, including temperature, heart rate, weight and systolic and diastolic blood pressure, will be presented in a by-patient listing. Blood pressure will be summarized as follows by treatment arm:

- Descriptive statistics, for systolic and diastolic blood pressure separately
    - Baseline value
    - Maximum on-treatment value
    - Change from baseline to maximum on-treatment value
- Categorical summary of baseline value, maximum on-treatment value for systolic and diastolic blood pressure separately, with categories defined as follows:
    - Diastolic blood pressure
        - <80 mm Hg
        - 80 – 89 mm Hg
        - 90 or higher mm Hg
    - Systolic blood pressure
        - <120 mm Hg
        - 120 – 129 mm Hg
        - 130 – 139 mm Hg
        - 140 or higher mm Hg
- Categorical summary of baseline value, maximum on-treatment value for systolic and diastolic blood pressure combined using the categories define above (*i.e.*, diastolic <80 mm Hg and systolic <120 mm Hg, diastolic <80 mm Hg and systolic 120 – 129 mm Hg)

Heart rate will be summarized as follows by treatment arm:

- Descriptive statistics for baseline value, minimum on-treatment value, maximum on treatment value, change from baseline to maximum on-treatment value
- Categorical summary of baseline value, minimum on-treatment value, maximum on-treatment value, with categories defined as follows:
    - <60 bpm
    - 60 – 100 bpm
    - <100 bpm

Plots of mean observed value over time will be produced for diastolic blood pressure, systolic blood pressure, heart rate and temperature.

5.3.4 ECOG Performance Status

A by-patient listing will be presented for ECOG performance status data.

5.3.5 Electrocardiogram (ECG)

A by-patient listing will be presented for ECGs. Per the protocol, ECGs are to be collected at baseline.

5.3.6 Echocardiogram

A by-patient listing will be presented for echocardiogram baseline and post-baseline assessments (if any)

5.3.7 Concomitant Medications and Procedures

Please refer to Section 5.1.6 for the definition and summary of concomitant medications. Concomitant procedures will not be summarized. A by-patient listing will be presented.

5.3.8 Deaths

On-treatment deaths are defined as deaths that occur within 30 days of the last dose of study medication. Deaths on treatment and causes for deaths occurring on treatment, deaths occurring prior to progression, and deaths during follow-up will be summarized.

A by-patient listing of deaths on study will be presented.

5.3.9 Pregnancy Test

A by-patient listing of pregnancy test results will be presented.

5.4 Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on the Safety Analysis Set.

Blood samples will be taken for the analyses of duvelisib and possible metabolite(s) in plasma at the time points defined in the schedule of assessments. The relevant PK parameters will be determined using bioanalytical data.

Presentation of PK data will include:

- Descriptive statistics (n, mean, standard deviation, %CV, median, minimum, maximum) will be presented in tabular form by cohort, cycle and day.
- Linear-linear and log-linear plots of mean and median by nominal time will be presented by cohort, cycle and day.

PK analysis will be repeated for the subset of enrolled Japanese patients and non-Japanese patients. The Japanese patients will be presented separately for the Safety run-in patients (first 6 Japanese patients treated) and expansion phase patients (remaining expansion phase Japanese patients).

5.5 Exploratory Endpoints

Descriptive statistics by visit will be presented for exploratory endpoints. The analyses of exploratory analyses may or may not be presented formally. Further details on these analyses may be outlined in a separate analysis plan, and results may be summarized in a separate report. Tumor biomarkers such as deoxyribonucleic acid (DNA) sequence variation, germline DNA sequence variations, DNA copy number variation, ribonucleic acid (RNA) expression, protein expression, and/or immune cell infiltrate will be evaluated using summary statistics for prognostic factors.

6 References

1. Cella D, Webster K, Cashy J, Kutikova L, Burgess MF, Lin BK, Bowman L, Liepa AM, Gauthier JE, Gregory SA, Johnson SA, Cheson BD. *Development of a measure of health-related quality of life for non-Hodgkin's lymphoma clinical research: the functional assessment of cancer therapy-lymphoma (FACT-Lym).* Blood 2005;106:750.
2. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, and Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-3067.

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: [redacted]
Title: [redacted]
Date: Wednesday, 30 August 2023, 08:44 PM GMT Standard Time
Meaning: Document contents approved.
==========