NCT #: NCT01882803

STATISTICAL ANALYSIS PLAN

IPI-145-06

A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma

Protocol Version:	**Amendment 3**
Type of Analysis Plan:	**Interim and Final Analyses**
Version:	**2.0**
Date:	**01 FEB 2016**
Author:	[redacted]

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

The undersigned has developed this statistical analysis plan:

Name/Title	Signature	Date
[redacted]		

Reviewed and approved by:

Name/Title	Signature	Date
[redacted]		

Document History

Version	Date	Author(s)	Brief Summary of Changes
1.0	30 Jun 2014	[redacted]	Original
2.0	01 Feb 2016	[redacted]	Update per protocol amendment 3 and add additional analyses

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice a Day/Twice Daily
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CHOP	Cyclophosphamide, Hydroxydaunorubicin, Oncovin® (vincristine), and Prednisolone
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, Vincristine, and Prednisolone
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EOT	End Of Treatment
EQ-5D	European Quality Of Life (Version 5D)
FAS	Full Analysis Set
FDA	Food And Drug Administration
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
IDMC	Independent Data Monitoring Committee

INR	International Normalized Ratio
IRC	Independent Review Committee
IWG	International Working Group
LFT	Liver Function Tests
LNR	Lymph Node Response
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal Zone Lymphoma
NCI	National Cancer Institute
(i)NHL	(Indolent) Non-Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PRwL	Partial Response with Lymphocytosis
PT (Coagulation)	Prothrombin Time
PT (MedDRA)	Preferred Term
aPTT	Activated Partial Thromboplastin Time
QoL	Quality of Life
QTcF	Fridericia-Corrected QT Interval
RNA	Ribonucleic Acid
RDI	Relative Dose Intensity
RIT	Radioimmunotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Stable Disease
SGOT	Serum Glutamic-Oxaloacetic Transaminase

SGPT	Serum Glutamic-Pyruvic Transaminase
SLL	Small Lymphocytic Lymphoma
SOC	System Organ Class
SPD	Sum of the Products of the Perpendicular Diameters
TEAE	Treatment Emergent Adverse Event
TTR	Time To Response
TTP	Time To Progression
ULN	Upper Limit Of Normal
UNK	Unknown
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed description of the statistical methods to be implemented for the analysis of the data collected in the IPI-145-06 study: *A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma* (iNHL).

This SAP is based on protocol amendment 3 (global), dated 03 Nov 2015.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the antitumor activity of IPI-145 administered to subjects diagnosed with iNHL (defined as follicular lymphoma [FL], marginal zone lymphoma [MZL; splenic, nodal and extranodal], or small lymphocytic lymphoma [SLL]) whose disease is refractory to rituximab and to either chemotherapy or radioimmunotherapy (RIT).

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To evaluate the safety of IPI-145 in all subjects
- To evaluate additional efficacy parameters in all subjects
- To evaluate the PK of IPI-145 and, if applicable, its metabolite(s)

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of the study are:

- To evaluate whether baseline values or treatment-related changes in biomarkers correlate with IPI-145 clinical activity, safety and/or resistance in iNHL.
- To evaluate whether tumor genomic or pharmacogenomic markers correlate with IPI-145 clinical activity, safety, PK and/or resistance in iNHL
- To evaluate the health-related quality of life (QoL) of subjects

3 STUDY DESIGN

3.1 OVERVIEW

Study IPI-145-06 is a Phase 2, open-label, single arm efficacy and safety study of IPI-145 administered orally to subjects diagnosed with iNHL (FL, MZL or SLL) whose disease is refractory to rituximab and to either chemotherapy or RIT. The study population consists of adult male and female subjects who meet the inclusion/exclusion criteria, enrolled at up to approximately 100 sites worldwide.

All subjects enrolled will be assigned to the same treatment of 25 mg IPI-145 orally twice daily (BID) administered continuously in 28-day treatment cycles for up to 13 cycles. To receive additional cycles of IPI-145 beyond 13 cycles, subjects must have documented evidence of response (CR or PR) or stable disease (SD) at the Cycle 14 Day 1 response assessment according to the revised International Working Group (IWG) criteria. These subjects may continue to receive IPI-145 treatment until disease progression or unacceptable toxicity.

All subjects who permanently discontinue treatment with IPI-145 for reasons other than withdrawal of consent from overall study participation will enter survival follow-up. Survival follow-up will occur every 6 months (±4 weeks) from permanently discontinuing IPI-145 treatment for up to 3 years after first dose of IPI-145 or until death.

3.2 SAMPLE SIZE CONSIDERATION

The primary endpoint of the study is overall response rate (ORR), as defined in Section 5.1. This study will test the null hypothesis that the ORR is ≤30% against the alternative that ORR is ≥45%. Using a group sequential design with 1 interim analysis, 120 subjects will provide >90% power to achieve a one-sided overall significance level of 0.025. The interim analysis will occur approximately 4 months after at least 30 subjects (25% of the total) have initiated treatment with IPI-145. The cumulative Type II error to be spent at the interim and final analyses are 0.02 and 0.1, respectively. The interim analysis is intended for futility only and hence no Type I error will be spent.

Among the 120 subjects to be enrolled, approximately 80 will be FL.

3.3 UNBLINDING

Not applicable. This is a single arm open label study.

3.4 INTERIM ANALYSIS

An interim futility analysis will be performed approximately 4 months after at least 30 subjects (25% of total) have initiated treatment with IPI-145. The futility boundary is

non-binding, meaning that the Type I error will be properly controlled if the study continues after the futility boundary is crossed at the interim analysis. If the interim analysis occurs 4 months after exactly 30 subjects have initiated treatment, the one-sided p-value for futility is 0.6552. This is equivalent to a response rate of 26.4% or 7 responders or less out of the 30 subjects. Actual p-value boundary for futility will be calculated based on the number of subjects at the interim analysis by linear interpolation.

ORR based on the Investigator's assessment will be used for the interim analysis.

If the required total number of subjects are accrued for the interim analysis but follow-up is not sufficiently mature to reasonably assess the ORR, accrual may proceed while the data on interim analysis subjects are being collated.

The following data will be reviewed by an external Independent Data Monitoring Committee (IDMC) at the interim analysis: ORR, time to response (TTR), disposition, demographics and baseline characteristics, prior anticancer therapy, medical history, concomitant medications, exposure, dose modifications, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, laboratory parameters, and additional data requested by the IDMC. Further details will be provided in the IDMC charter.

4 ANALYSIS SETS

4.1 FULL ANALYSIS SET

The Full Analysis Set (FAS) will include all subjects who have been treated with at least one dose of IPI-145. The FAS will be the primary analysis set for all efficacy and safety analyses.

4.2 EVALUABLE ANALYSIS SET

The Evaluable Analysis Set (EAS) will include all subjects who meet the following criteria:

- Remain in the treatment phase of the study for at least 8 weeks or have a documented disease progression per revised IWG criteria before 8 weeks of treatment
- Have an adequate baseline tumor assessment (at least one nodal target lesion ≥1.5 cm in the longest diameter)
- Have at least 1 adequate post baseline tumor assessment unless death due to disease progression
- No major protocol deviations that could have an impact on efficacy (The following list is phrased in terms of deviations. Subjects meeting these conditions will be excluded from the EAS):
    - Have not been diagnosed with indolent NHL [FL, MZL or SLL] (inclusion criterion #2)
    - Do not have disease that is refractory to a chemotherapy induction regimen or RIT (inclusion criterion #3)
    - Do not have disease that is refractory to rituximab (inclusion criterion #4)
    - Prior treatment with any PI3K inhibitor or Bruton's Tyrosine Kinase (BTK) inhibitor (exclusion criterion #2)
    - Grade 3B FL and/or clinical evidence of transformation to a more aggressive subtype of lymphoma (exclusion criterion #7)
    - Have been taking other anticancer therapies during the treatment phase of the study that could seriously confound the effects of the study treatment

The EAS will be a secondary analysis set for selected efficacy analyses.

5 STUDY ENDPOINTS AND OTHER VARIABLES

5.1 PRIMARY ENDPOINT

The primary endpoint for the study is ORR, with overall response defined as best response of complete response/remission (CR) or partial response/remission (PR), according to the revised IWG Criteria.

ORR will be derived from best overall response (BOR), which is defined as the best time-point response that a subject achieves during the course of the study, with the response ranked according to the following order (from best to worst): CR>PR>SD>PD. In addition, a subject who does not have an adequate baseline assessment or who does not have any adequate post-baseline response assessment will have a BOR of unknown (UNK). A subject who has an adequate baseline assessment that shows no evidence of disease and who does not have a post-baseline assessment of PD will have a BOR of no evidence of disease (NED).

5.2 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints of the study are:

- Duration of response (DOR) defined as the time from the first documentation of response to the first documentation of progressive disease (PD) or death due to any cause
- Progression-free survival (PFS) defined as the time from the first dose of study treatment to the first documentation of PD or death due to any cause
- Overall survival (OS) defined as the time from the first dose of study treatment to the date of death
- Time to response (TTR), defined as the time from the first dose of study treatment to the first documentation of response (complete or partial)

5.3 EXPLORATORY EFFICACY ENDPOINT

The exploratory efficacy endpoint of this study is:

- Lymph node response rate (LNR rate), with LNR defined as ≥50% reduction in the Sum of the Products of the Perpendicular Diameters (SPD) of nodal target lesions

5.4 SAFETY ENDPOINTS

The Safety endpoints include treatment-emergent adverse events (TEAEs), ECG measures, and changes in safety laboratory values.

5.5 PHARMACOKINETIC ENDPOINTS

Pharmacokinetics endpoint of the study is:

- PK parameters derived from plasma IPI-145 concentrations and, if applicable, its metabolite(s)

5.6 BIOMARKER ENDPOINTS

Biomarker endpoints of the study are:

- Serum, plasma and tissue biomarkers, and blood immunophenotype
- Tumor genomic features (e.g. DNA sequence variation, DNA copy number variation, and/or RNA expression)
- Germline DNA sequence variations

5.7 QUALITY OF LIFE ENDPOINTS

Health-related QoL of subjects as assessed by the following subject-reported questionnaire:

- EuroQol-5D (EQ-5D), a standardized instrument for use as a measure of health-related QoL

6 GENERAL STATISTICAL METHODS AND DATA HANDLING

6.1 GENERAL METHODS

Unless otherwise specified, categorical variables will be presented as frequencies and percentages, and continuous variables will be presented with the number of non-missing values, mean, standard deviation, median, minimum and maximum values. Graphs may also be presented where appropriate.

6.2 HANDLING OF MISSING DATA

For the purpose of calculating the duration from iNHL diagnosis or last anticancer therapy completion, partial/missing dates for iNHL diagnosis date and last anticancer therapy completion date will be imputed as follows:

- If both date and month are missing and the year is prior to the year of screening, the imputed date and month will be 01 July.
- If both date and month are missing and the year is the same as the year of screening, the imputed date will be the middle point between 01 Jan 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 date is missing and the month and year are prior to the month and year of screening, the imputed date will be 15th day of the month.
- If date 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 date 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.

Details on handling partial/missing dates for AE and concomitant medications are provided in Section 7.

6.3 MULTIPLE COMPARISONS/MULTIPLICITY

Not applicable for this study.

6.4 ADJUSTMENTS FOR COVARIATES

Adjustments for covariates will not be performed for this study.

6.5 SUBGROUPS

The primary endpoint and some secondary efficacy endpoints will be summarized by lymphoma subtypes. Details are available in Section 7.2. In addition, the primary endpoint will be analysed for the following subgroups:

- Number of prior therapies (<3 or ≥3)
- Number of prior therapies (1 or >1)
- Prior treatment with bendamustine (Yes or No)
- Refractory to bendamustine (Yes or No)
- Prior treatment with bendamustine-rituximab (Yes or No)
- Refractory to bendamustine-rituximab (Yes or No)
- FL subjects received only 1 prior therapy of bendamustine-rituximab and is refractory
- Refractory to last therapy status (Yes or No)
- Last therapy contains bendamustine and is refractory (Yes or No)
- Bulky status (Longest diameter of baseline lesion <5cm or ≥ 5cm)
- Gender (Male or Female)
- Age group (<65 or ≥65 years)
- Race (White or Non-White)
- Region (US or Non-US)

Refractory is defined as lack of a CR or PR on therapy or initiation of next therapy within 6 months (+ 30 days) of last dose.

6.6 METHODS OF POOLING DATA

No pooling will be performed for this study.

6.7 VISIT WINDOWS

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

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 subject
- 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

6.8 UNSCHEDULED VISITS

Unscheduled visits will only be included in listings and in post-baseline summaries of extreme values. Unless otherwise specified, unscheduled visits will not be included in the by-visit summaries.

6.9 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	MedDRA Version 16.1 or higher
Medical Histories	MedDRA Version 16.1 or higher
Prior and Concomitant Medications	WHODrug Version September 2013
Prior and post Systemic Therapy	WHODrug Version September 2013
Grading	
AEs	CTCAE Version 4.03
Laboratory Results	CTCAE Version 4.03

7 STATISTICAL ANALYSES

7.1 STUDY SUBJECTS

7.1.1 Disposition of Subjects

The number and percentage of subjects in each analysis set will be provided. This includes the FAS and the EAS. The percentage will be based on the number of subjects in the FAS.

Disposition of subjects will be summarized for the FAS. The number and percentage of subjects will be provided for those who are on treatment, those who discontinue treatment but are still in follow-up, and those who discontinue from the study. Further, subjects who discontinue treatment and those who discontinue from the study will each be summarized by reason for discontinuation. Disposition of subjects will be summarized for the overall population as well as by different disease subtypes.

Follow-up time (from 1st dose to last contact on or prior to data cut-off) will be descriptively summarized.

7.1.2 Demographic and Other Baseline Characteristics

Demographic characteristics include age, age category (<65 and ≥65), sex, race and ethnicity. Baseline characteristics include ECOG performance status, height, weight and BMI. These will be summarized for the FAS.

Disease diagnosis and staging will be summarized for both the FAS and EAS as follows: Translocations, FLIPI score at Screening, elevated LDH, Disease sub-type, NHL staging at diagnosis, NHL staging at entry, time from initial diagnosis to first dose date, baseline B-symptomatology, presence of bulky disease at baseline (any lymph node ≥5cm) and baseline cytopenia (≥Grade 3 neutropenia, ≥Grade 3 anemia, ≥Grade 3 thrombocytopenia). The imputation of partial/missing dates for time from initial diagnosis is provided in Section 6.2. Presence of bulky disease is not directly collected and will be derived based on measurements of target lesions.

Demographics and baseline characteristics will be summarized for the overall population as well as by different disease subtypes.

7.1.3 Medical History

Medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT), and sorted alphabetically in SOC and by decreasing frequency in PT. Medical history will be presented for the FAS.

7.1.4 Prior Therapies and Surgeries

Prior anticancer therapies will be summarized by ATC level 1, ATC level 2 and preferred drug name. Number of prior anticancer regimens (continuous and categorical) will be descriptively summarized.

The number and percentage of subjects treated with the following therapies will be provided: rituximab, rituximab induction monotherapy, bendamustine, alkylating agent, purine analogue, radioimmunotherapy, anthracycline, bendamustine-rituximab, combination of rituximab and alkylating agent, R-CHOP, R-CVP, and stem-cell transplant. The number and percentage of subjects who are refractory to the following therapies will be provided: rituximab, bendamustine, alkylating agent, purine analogue, radioimmunotherapy, anthracycline, bendamusitne-rituximab, combination of rituximab and alkylating agent, R-CHOP, and R-CVP. Subjects who are refractory to 2 or more regimens and subjects who are refractory to last therapy will also be provided. The definition of refractory is provided in Section 6.5.

Time since completion of last anticancer therapy to the first dose date will be summarized. Time since completion of the last rituximab therapy to the first dose date, and time since completion of last alkylating agent/purine analogue therapy to the first dose date will also be summarized. The imputation of partial/missing dates is provided in Section 6.2.

Prior radiation and prior surgeries (Yes and No) will be presented.

Prior therapies, radiation and surgeries will be summarized for the FAS.

Prior therapies will be summarized for the overall population as well as by different disease subtypes.

7.1.5 Prior and Concomitant Medications

Prior medications are defined as medications that stopped prior to the first dose of study drug.

Concomitant medications include either of the following:

- Medications that started on or after the first dose date of study drug, up to 30 days post last dose.
- Medications that started prior to and continued after the first dose of study drug.

Both prior medications and concomitant medications will be summarized by ATC level 1, ATC level 2 and preferred drug name. The summary will be sorted by decreasing frequency in ATC level 1, ATC level 2 and preferred drug name. A subject taking the same drug multiple times will only be counted once.

No imputation will be performed for missing/partial onset or stop dates. Partial dates will be used if they are sufficient to determine whether medications are prior or concomitant. Otherwise, medications with partial onset and/or stop dates will be considered as concomitant. Medications with completely missing dates will be considered as concomitant.

7.1.6 Exposure to Study Drug

Extent of exposure to study drug will be characterized by:

- Total actual dose (mg) calculated as: Sum of all doses received throughout the study
- Duration (months) calculated as: (Last dose date – first dose date + 1) divided by 30.4375
- Dose Intensity (mg/day) calculated as: Total actual dose divided by duration in days
- Relative dose intensity (%) calculated as: Dose intensity divided by the intended dose intensity multiplied by 100. The intended dose intensity is 50 mg/day because the starting dose is 25 mg BID.
- Compliance rate (%) calculated as: total actual dose divided by the total prescribed dose multiplied by 100. The total prescribed dose is the sum of all doses prescribed throughout the study.

Total actual dose, duration (continuous and categorical), dose intensity, relative dose intensity and compliance rate will be descriptively summarized. The total number of cycles started (continuous and categorical) will also be provided. In addition, time on treatment phase, defined as time from first dose to date of decision to discontinue treatment will be provided.

Dose modification is characterized by dose reduction, dose interruption and dose increase. If the current non-zero prescribed dose level is lower (or higher) than the immediately preceding non-zero prescribed dose level, it is considered as a dose reduction (or increase), regardless of the dosing history prior to the immediately preceding dose. The number of dose reductions (1, 2, ≥3), dose interruptions (1, 2, ≥3) and dose increases (1, 2, ≥3) will be summarized. Dose reductions and interruptions due to adverse events as provided from the Active Treatment eCRF will be similarly summarized.

Exposure and dose modification will be summarized for the overall population as well as by different disease subtypes.

7.1.7 Protocol Deviations

Protocol deviations will be finalized prior to database release for the final analysis. Major protocol deviations will be summarized by type of deviation for the FAS. A listing will be provided for all major protocol deviations.

7.2 EFFICACY ANALYSES

Assessment of response and progression status will be evaluated locally (i.e. Investigator's assessment) and by an independent, third party panel of radiologists and oncologists (Independent Review Committee [IRC]) according to the revised IWG Response Criteria for Malignant Lymphoma[1]. The IRC assessment will be used for the primary analyses of response and progression-based efficacy endpoints (e.g., ORR, PFS, TTR and DOR). Data based on local assessment will also be presented for these endpoints.

7.2.1 Analysis of Primary Efficacy Endpoint

7.2.1.1 *Primary Analysis*

ORR will be tested against the null (≤30%) by 1-sided exact binomial test at 0.025 level. The estimated ORR (percent of subjects with a BOR of CR or PR), a 2-sided 95% exact confidence interval and the p-value will be provided. Number and percentage of subjects with BOR in each of the response categories (CR, PR, SD, PD, NED and UNK) will also be presented. All subjects in the analysis set will be included in the denominator in the calculation of the percentage for each response category or ORR. In other words, missing data will be imputed for the calculation of ORR by assuming that any subjects not exhibiting a response (CR or PR) are non-responders.

Best overall response (BOR) and ORR will be presented for the overall population. They will also be presented for the FL population, as well as other disease subtypes (MZL and SLL). For each disease subtype, the summary will be the same as that for the overall population except that the hypothesis test will not be performed.

ORR will be analysed for the subgroups provided in Section 6.5. These subgroup analyses will also be performed similarly for FL subjects. A forest plot of ORR for different subgroups will also be provided.

Listings of data to support response assessment, including lesions with dimensions, liver/spleen assessments, bone marrow and B symptoms will be provided.

These analyses will be performed for the FAS and the EAS with FAS being the primary analysis set.

7.2.1.2 *Sensitivity Analysis*

The revised IWG criteria does not take lymphocytosis into account. As a sensitivity analysis, subjects that have a BOR of PR with lymphocytosis (PRwL) will be excluded from the numerator in the calculation of ORR. The denominator will be the same as that for the primary analysis of ORR.

PRwL is defined as:

- CR or PR per revised IWG criteria, and

- Lymphocytes meeting both of the following
  - ≥ 4,000/μL
  - No decrease from baseline or decrease from baseline for less than 50%.

The lymphocyte count considered here should be within +/- 7 days of the IWG response assessment. If multiple lymphocyte counts are available, the one that is closest to the date of IWG response assessment will be used.

The IWG response used to determine PRwL will be based on the IRC assessment. Lymphocytes will be integrated into this algorithm programmatically. This analysis will be performed for SLL subjects in the FAS.

7.2.2 Analyses of Secondary Efficacy Endpoints

7.2.2.1 *Progression Free Survival (PFS)*

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

PFS will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median PFS will be provided. PFS will be analysed for the FAS and the EAS with FAS being the primary analysis set. It will also be analysed for the follicular lymphoma population, as well as the other disease subtypes within the FAS.

Table 2: PFS and DOR censoring algorithm

Situation	Date of Event or Censoring	Outcome
No adequate baseline disease status assessment	Date of first dose	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of first dose + 1	Censored
No documented progression or death before data cutoff	Date of last adequate disease status assessment	Censored

Situation	Date of Event or Censoring	Outcome
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 long gap between adequate disease status assessments (e.g., 2 or more consecutive missed scheduled disease status assessments along with a gap of more than 6 months)	Date of last adequate disease status assessment before the gap	Censored
New anticancer treatment or procedure started before documented progression	Date of last adequate disease status assessment	Censored

Note: the first two rows are applicable to PFS only.

7.2.2.2 *Duration of Response (DOR)*

The censoring algorithm provided in Table 2 above will also be used for DOR. Because DOR is only analysed for responders, the first two rows are not applicable. DOR will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median DOR will be provided. DOR will only be analysed for responders (CR or PR).

DOR will be analysed for the FAS and the EAS with FAS being the primary analysis set. It will be analysed for the FL population, as well as the other disease subtypes within the FAS. DOR will also be analysed for the following subgroups:

- FL subjects who received only 1 prior treatment of BR and is refractory
- Number of prior therapies (<3 or ≥3)
- Prior treatment with bendamustine (Yes or No)
- Refractory to bendamustine (Yes or No).

7.2.2.3 *Overall Survival (OS)*

Subjects who are last known to be alive will be censored at date of last contact. OS will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median OS (if reached) will be provided. OS will be analysed for the FAS and the EAS with FAS being the primary analysis set. It will also be analysed for the FL population, as well as the other disease subtypes within the FAS.

7.2.2.4 *Time to Response (TTR)*

TTR (continuous and categorical) will be descriptively summarized for responders (CR or PR) only. TTR will be analysed for the FAS and the EAS with FAS being the primary analysis set. It will also be analysed for the FL population, as well as the other disease subtypes within the FAS.

7.2.3 Analyses of Exploratory Efficacy Endpoint

7.2.3.1 *LNR Rate*

The estimated LNR rate will be provided together with a 2-sided 95% confidence interval. A waterfall plot of the best percent change in the SPD of nodal target lesions will also be provided. Only subjects with baseline and post-baseline nodal target lesion measurements will be included in the plot.

LNR rate will be analysed for the FAS and the EAS with FAS being the primary analysis set. It will also be analysed for the FL population, as well as the other disease subtypes within the FAS.

7.3 SAFETY ANALYSES

Unless otherwise specified, all safety analyses will be performed for the overall population as well as by different disease subtypes in the FAS.

7.3.1 Adverse Events

Adverse events (AEs) will be graded by the Investigator using the NCI-CTCAE version 4.03 where possible. If an AE is not included in the NCI-CTCAE version 4.03, the Investigator will grade the AE according to the algorithm outlined in Section 8.2.1.2 of the protocol. In the case of multiple AE occurrences of the same MedDRA PT within a subject, the most severe grade observed will be reported when displaying AEs by grade. AEs with a relationship to study drug flagged as ‘None’ or ‘Remote’ will be considered ‘Not Treatment-Related’. AEs with a relationship of ‘Possible’, ‘Probable’, or ‘Definite’ will be considered ‘Treatment-Related’. In the event that multiple AEs of the same MedDRA PT with different relationship assignments exist for a study subject, the most conservative relationship will be reported when displaying AEs by relationship.

Treatment-emergent adverse events (TEAE) will be tabulated. A TEAE is defined as any AE that emerges or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment. The onset date of an adverse event will be compared to the first dose date and the last dose date plus 30 days to determine if the AE is treatment-emergent or not. If a partial date is adequate to determine when the onset date of an event occurred relative to first dose of study medication and the last dose date plus 30 days, then the partial date will be used. If a partial date does not provide enough information to determine the onset date relative to first dosing date and the last dose date plus 30 days, the adverse event will be assumed as treatment-emergent.

Adverse events (AEs) will be summarized by MedDRA SOC and PT, PT only, or SOC only. For summary tables by SOC and PT, SOC will be sorted alphabetically and PT will be sorted by decreasing frequency for the overall column within each SOC. For summary tables by PT only, PT will be sorted by decreasing frequency for the overall column.

Summaries (number and percentage of subjects) will be provided as follows:

- Overview of TEAEs
- TEAE by MedDRA SOC and PT
- TEAE by MedDRA SOC and PT – treatment-related
- TEAE by MedDRA SOC, PT for maximum grade ≥ 3
- TEAE by MedDRA SOC, PT for maximum grade ≥ 3 – treatment-related
- TEAE by MedDRA PT
- TEAE by MedDRA PT – treatment-related
- TEAE by MedDRA PT for PTs of grade ≥ 3
- TEAE by MedDRA SOC, PT and maximum grade
- TEAE by MedDRA SOC, PT and maximum grade – treatment-related
- Treatment-emergent SAEs by MedDRA SOC and PT
- Treatment-emergent SAEs by MedDRA SOC and PT – treatment-related
-
- Treatment-emergent SAEs by MedDRA PT
- Treatment-emergent SAEs by MedDRA PT – treatment-related
- TEAE by MedDRA SOC and PT resulting in death
- TEAE by MedDRA SOC and PT resulting in death – treatment-related
- TEAE by MedDRA SOC and PT resulting in study drug interruption
- TEAE by MedDRA SOC and PT resulting in study drug dose reduction
- TEAE by MedDRA SOC and PT resulting in study drug interruption or dose reduction
- TEAE by MedDRA SOC and PT resulting in study drug discontinuation
- TEAE by MedDRA SOC and PT resulting in study drug discontinuation – treatment-related

- Deaths on treatment (defined as on treatment or within 30 days of last dose)
- Deaths in follow-up (defined as deaths occurring >30 days after last dose)

Listings will be provided for the following:

- All Adverse Events
- Serious Adverse Events
- AEs resulting in study drug interruption
- AEs resulting in study drug reduction
- AEs resulting in study drug discontinuation
- Deaths on study (all-cause mortality, table structured as a listing)
- AEs resulting in death (table structured as a listing)

7.3.2 Laboratory Data

Clinical laboratory assessments for this study include: hematology, blood chemistry including liver function tests (LFTs), coagulation, urinalysis and immunoglobulin. Values will be analysed after conversion into standard international units, where applicable. A complete listing of all laboratory parameters with normal ranges is included in Appendix 1.

Applicable laboratory data will be graded according to NCI-CTCAE Version 4.03. Shift from baseline to maximum post-baseline grades will be tabulated for hematology, blood chemistry including liver function test (LFT), and coagulation.

Post-baseline lab values used in summary tables for shift in grades, and LFT elevations will include lab tests performed after the start of the first dose of study treatment, up to 30 days post last dose.

Laboratory parameters will be presented as follows:

- Shift from baseline to maximum post-baseline CTCAE grade for hematology laboratory parameters
- Shift from baseline to maximum post-baseline CTCAE grade for chemistry laboratory parameters
- Shift from baseline to maximum post-baseline CTCAE grade for coagulation laboratory parameters
- New grade ≥3 hematology laboratory parameters
- New grade ≥3 chemistry laboratory parameters
- By visit summary of change from baseline for immunoglobulin parameters

- Listing of subjects with AST or ALT >3xULN in combination with total bilirubin >2xULN. The elevations of ALT/AST and total bilirubin must occur within 2 days of each other.
- Listing of all laboratory values
- Listing of laboratory parameters with grade 3 or higher CTCAE grades.
- Listing of selected hematology laboratory parameters with CTCAE grades
- Listing of selected LFTs with CTCAE grades

7.3.3 Vital Signs

Vital signs will be presented in individual subject data listings, and will not be summarized by visit.

7.3.4 Electrocardiogram (ECG)

ECG data and change from baseline will be descriptively summarized by visit. The frequency and percentage of subjects meeting the following criteria will be summarized by visit:

- QTcF (msec) categorized as:
  - ≤ 450
  - > 450 to ≤ 480
  - > 480 to ≤ 500
  - > 500
- Change from baseline in QTcF (msec):
  - ≤ 30
  - > 30 to ≤ 60
  - > 60

Subjects' QTcF values for each of the summaries above will be the arithmetic mean of the triplicate measures taken at each respective timepoint.

7.4 PHARMACOKINETIC ANALYSES

Plasma samples will be analyzed for IPI-145 and potential metabolite concentrations using a validated high performance liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. A summary table and a listing of IPI-145 and IPI-656 concentrations will be provided. The PK data collected will be analyzed by standard population PK methods, using appropriate software. Analysis of exposure-response relationships for efficacy and safety endpoints will be conducted. If there is only a limited amount of plasma concentration data from this study, the data may be pooled with the results of other studies to perform the population PK and exposure-response analyses. Further details on these analyses will be outlined in a separate analysis plan.

Results of the population PK and exposure-response analysis will be summarized in a separate technical report.

7.5 BIOMARKER ANALYSES

Biomarkers measured in serum, plasma, blood and tumor tissues will be analyzed in an exploratory fashion. These exploratory analyses may or may not be presented formally. If presented, they will be limited to biomarkers for which data from a sufficient number of subjects are available.

7.6 QOL ANALYSES

EQ-5D data will be summarized for the FAS by visit. The number and percentage will be presented for each question/domain, and summary statistics will be provided for the health status score.

8 CHANGES IN PLANNED ANALYSES

8.1 CHANGES IN PLANNED ANALYSES FROM PROTOCOL AMENDMENT 1 TO SAP V1.0

No change is made in the planned analyses from protocol amendment 1 to SAP V1.0.

8.2 CHANGES IN PLANNED ANALYSES FROM SAP V1.0

SAP Version	Section	Summary of Change	Reason for Change
2.0	3.2	Change the number of FL subjects	Update per Protocol Amendment 2
2.0	3.4	Change internal DMC to external IDMC	Update per Protocol Amendment 2
2.0	5.3	Remove CR as an exploratory endpoint	Update per Protocol Amendment 3
2.0	6.5	Definition of refractory	Be consistent with entry criteria
2.0	6.5	Add additional subgroup analysis for the primary endpoint	Better understand the performance of Duvelisib
2.0	7.1.4	Add analysis of specific prior therapies	Better characterise patient population
2.0	7.2.2.3	Add analysis of OS rate at 12 months	Needed as the median may not be available at the time of primary analysis
2.0	7.2.2.4	Change the analysis method for TTR	TTR can be summarized descriptively as no censoring is involved
2.0	7.3.2	Change the presentation of some lab data	Better present lab data

9 REFERENCES

Cheson BD, Pfistner B, Juweid ME et al. Revised Response Criteria for Malignant Lymphoma. J Clin Onc. 2007; 25(5):579-86.

10 APPENDIX

Appendix 1 Summary of Laboratory Parameters and Associated Normal Ranges

Lab Type	Parameter	Textbook Reference Range	Unit
Hematology	WBC/Leukocytes*	4.5-11.0	10^3/uL
	Hemoglobin*	Male: 13.5-17.5 Female: 12.0-16.0	g/dL
	Hematocrit	Male: 41.00-53.00 Female: 36.00-46.00	%
	Platelets*	150-350	10^3/uL
	Lymphocytes	22-44	%
	Neutrophils	40-70	%
	Eosinophils	0-8	%
	Monocytes	4-11	%
	Basophils	0-3	%
	Lymphocytes*	1.2-3.4	10^3/uL
	Neutrophils*	3-5.8	10^3/uL
	Eosinophils	0-0.7	10^3/uL
	Monocytes	0.11-0.59	10^3/uL
	Basophils	0-0.2	10^3/uL
	ANC*	3-5.8	10^3/uL
Blood Chemistry	Glucose*	75.00-115.00	mg/dL
	BUN	10.00-20.00	mg/dL
	Serum creatinine*	0-1.5	mg/dL
	Sodium*	136-145	mEq/L
	Potassium*	3.5-5.0	mEq/L
	Chloride	98-106	mEq/L
	Bicarbonate	21-30	mEq/L

	Carbon dioxide	21-30	mEq/L
	Calcium*	9.0-10.5	mg/dL
	Total Protein	5.5-8.0	g/dL
	Albumin*	3.5-5.5	g/dL
	Phosphorus*	3.0-4.5	mg/dL
	Magnesium*	0.74-1.23	mmol/L
	Lipase*	0-160	U/L
	Amylase*	60-180	U/L
	Uric acid*	Male: 2.5-8.0 Female: 1.5-6.0	mg/dL
Liver Function Tests	ALT(SGPT)*	0-35	U/L
	AST(SGOT)*	0-35	U/L
	Alkaline phosphatase*	30-120	U/L
	Direct bilirubin	0.10-0.30	mg/dL
	Total Bilirubin*	0.30-1.00	mg/dL
	LDH	100-190	U/L
Coagulation	PT	11.1-13.1	sec
	aPTT*	22.1-35.1	sec
	INR*	0.9-1.1	No Unit
Immunoglobulins	IgA	60-309	mg/dL
	IgE	10-179	IU/mL
	IgG	614-1295	mg/dL
	IgM	53-334	mg/dL

*Indicates CTCAE Gradable