Title:	An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma
Protocol Number:	ACE-LY-004
Version Number:	0.0
Version Date:	15 March 2017

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas

PPD

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Date

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Statistical Analysis Plan

An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma

Protocol Number: ACE-LY-004

Version:	**Version 0.0**
Date:	**15 March 2017**
Study Statistician:	PPD

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TABLE OF ABBREVIATIONS

AE(s)	adverse event(s)
ALC	absolute lymphocyte count
AMA	American Medical Association
BID	twice per day
CI	confidence interval
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone
DOL	duration of lymphocytosis
DOR	duration of response
ECG	electrocardiogram
ECI	adverse event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capturing
EORTC	European Organisation for Research and Treatment of Cancer
GI	gastrointestinal
HBV	hepatitis B virus
IRC	Independent Review Committee
IPD	important protocol deviation
ISS	Integrated Summary of Safety
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LDHULN	LDH relative to upper limit of normal
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	MCL international prognostic index
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction

PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PR	partial response
CCI [redacted]	
PT	preferred term
QD	once per day
QLQ-C30	Core Quality of Life Questionnaire
QTc	corrected QT interval
R/R	relapsed/refractory
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
TEAE(s)	treatment-emergent adverse events
CCI [redacted]	
US	United States
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within Protocol Amendment 6 for Study ACE-LY-004, which is entitled "An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma" dated 19 July 2016. Any changes to the methods described in the final SAP will be documented in the clinical study report (CSR). Hereafter, acalabrutinib (a generic name for ACP-196) will be used in place of ACP-196 in this document.

Separate reports will be generated for pharmacokinetic (PK) and pharmacodynamic data.

2 OBJECTIVES

2.1 Primary Objectives

- To determine the activity of acalabrutinib in subjects with relapsed/refractory (R/R) mantle cell lymphoma (MCL) as measured primarily by response rate. In addition, activity of acalabrutinib will be assessed by duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

2.2 Secondary Objectives

- To characterize the safety profile of acalabrutinib
- To characterize the PK profile of acalabrutinib
- To evaluate the PD effects of acalabrutinib

3 STUDY OVERVIEW

3.1 Study Design

This clinical trial is a phase 2, multicenter (approximately 70 global centers), open-label study in subjects with histologically documented MCL, who have relapsed after or were refractory to ≥1 (but not >5) prior treatment regimens. Subjects will be enrolled and will take 100 mg of acalabrutinib twice per day (bid) in repeated 28-day cycles.

Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity, whichever occurs first. Dose modification provisions are provided in the study protocol. All subjects who discontinue study drug will have a safety follow-up visit 30 (+7) days after the last dose of acalabrutinib. An early

termination visit is required for any subjects who permanently discontinued study drug for any reason including disease progression (exceptions included death, lost to follow-up, or withdrawal of consent).

All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2, every 4 weeks in Cycles 3 to 12, and every 12 weeks thereafter. PK/PD testing will be done in Cycles 1 and 2. Tumor assessments will be completed at 8- to 12-week intervals during the trial.

The primary efficacy analyses will be based on investigator assessment. An Independent Review Committee (IRC) will assess the efficacy endpoints in accordance with the IRC charter provided separately from this document.

3.2 Sample Size

The study will enroll approximately 117 subjects.

A one-sample Chi-square test with a 0.025 1-sided significance level will have more than 99% power to test the null hypothesis that overall response rate (ORR) will be ≤20% (not considered clinically compelling) versus the alternative hypothesis that ORR will be ≥40%. The sample size will also provide adequate estimation utility for safety and other secondary analyses. In particular with a sample size of 117 subjects, the probability of observing 1 or more instances of a specific adverse event (AE) with a true incidence rate of 1%, 2% or 5% is 69.1%, 90.6%, or 99.8%, respectively. This provides reasonable assurance that events occurring at ≥1% frequency can be identified in this Phase 2 study.

EAST6 (Version 6.3.1) was employed to conduct the sample size calculation.

4 STUDY ENDPOINTS

4.1 Primary Endpoints

The primary endpoint of the study is the ORR, defined as the proportion of subjects achieving either a partial response (PR) or complete response (CR) per the Lugano classification for non-Hodgkin lymphoma (NHL) (Cheson 2014) (hereafter referred to as Lugano classification) as assessed by investigators.

FDA provided the feedback that ORR by IRC should be used as primary endpoint for labeling purposes via Type C Content and Format meeting for the MCL New Drug Application (NDA). Since the study was conducted with investigator assessed ORR per Lugano classification as the primary endpoint, the SAP will retain the investigator primary to be consistent with the protocol. To meet labeling needs, both IRC and investigator assessed ORR will be analyzed in the same fashion, i.e., all planned analyses for the investigator assessed ORR will also be provided for the IRC assessed ORR per Lugano classification.

4.2 Secondary Endpoints

4.2.1 Efficacy

- DOR per Lugano classification as assessed by investigators
- PFS per Lugano classification as assessed by investigators
- OS
- IRC-assessed ORR, DOR, and PFS per Lugano classification

4.2.2 Safety

- Frequency and severity of AEs/SAEs
- Frequency of AEs requiring discontinuation of study drug or dose reductions
- Effect of acalabrutinib on peripheral T/B/natural killer (NK) cell counts
- Effect of acalabrutinib on serum immunoglobulin levels

4.2.3 Pharmacokinetics

- Plasma pharmacokinetics of acalabrutinib

4.3 Exploratory Endpoints

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

5 HYPOTHESES AND MULTIPLICITY

No formal statistical hypotheses will be tested. The clinical hypotheses are that acalabrutinib monotherapy is safe and effective in subjects with R/R MCL.

6 ANALYSIS SUBSETS

6.1 All-treated Population

The safety analyses and primary efficacy analyses for all efficacy endpoints will be performed on the All-treated Population, defined as all enrolled subjects who receive ≥1 dose of study drug. The analyses of DOR and CCI will be conducted on the subset of the All-treated Population who achieve CR or PR as their best overall response.

6.2 Subgroup Analysis

Subgroup analysis will be performed for ORR and CR per Lugano classification as assessed by investigators using the following baseline variables:

- Age (<65 years versus ≥65 years; <75 years versus ≥75 years)
- Sex (male versus female)
- Race (White versus non-White)
- Ann Arbor staging for lymphoma (1-3 versus 4)
- Simplified MCL international prognostic index (MIPI) (low risk [0 to 3] versus intermediate risk [4 to 5] versus high risk [6 to 11])
- Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 versus ≥2)
- Bone marrow involvement (yes/no)
- Extranodal disease (yes/no)
- Tumor bulk (largest diameter) (<5 cm versus ≥5 and <10 cm versus ≥10 cm)
- Refractory disease (yes/no)

- Gastrointestinal disease (yes/no)
- Prior number of regimens (1 versus 2 versus ≥3)
- Prior proteasome inhibitor (yes/no)
- Prior stem cell transplant (yes/no)
- Prior hyper CVAD regimen: cyclophosphamide, vincristine, doxorubicin, dexamethasone (yes/no)
- Prior lenalidomide (yes/no)
- Region (United States [US] versus Ex-US)

7 INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

Prior to Protocol Amendment 4.0, dated 14 November 2015, the protocol consisted of 2 parallel cohorts (bortezomib-naive and the bortezomib-exposed) each based on a Simon's 2 stage design. Subjects who received at least two cycles of other commercially available proteasome inhibitors (eg. carfilzomib) were enrolled into the bortezomib-exposed cohort.

An interim analysis for futility based on response rate was performed in September 2015 per Protocol Amendment 3 (dated 17 July 2015). In this interim analysis, within the first 28 patients enrolled to bortezomib-naive cohort, the required response rate for continuation (≥8/28 responders) was exceeded. Within the first 12 subjects enrolled to the bortezomib-exposed cohort, the required response rate for continuation (≥3/12 responders) was also exceeded. Based on this interim analysis, enrollment to both study cohorts could continue without interruption.

The protocol was amended in November 2015 (Protocol Amendment 4.0) based on emerging data that support the merging of the 2 cohorts by prior bortezomib exposure. The Phase 2 study of ibrutinib in R/R MCL reported similar overall response rates in the bortezomib-naive and bortezomib-exposed subjects (68% and 67%, respectively) (Wang 2013), indicating that prior bortezomib exposure does not appear to influence response to Btk inhibitor therapy. This is further supported by emerging data from this study (ACE-LY-004). The study will retain the original planned sample size of 117 subjects to obtain adequate safety and exposure data with acalabrutinib in this patient population.

The futility analysis is not expected to have any meaningful impact on the final analysis of this study; therefore, no adjustment will be made.

8 FINAL ANALYSIS AND CLINICAL STUDY REPORT

The final analysis of primary and secondary efficacy endpoints will occur approximately 14 months after the last subject has been enrolled. A follow-up analysis will be performed when all subjects have completed their study participation. The CSR will be written based on the final analysis and the CSR addendum will be written at the time of follow-up analysis.

9 MISSING VALUES

9.1 Safety Data

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15th of the month will be used.
- If only year is present, then June 30th will be used.

If such imputation date for initial diagnosis is on or after date of first dose, the date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before the date of last dose, the date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as the first dose date but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, the date of death will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

9.2 Efficacy Data

The method for handling missing data is described in the definition for each of the efficacy endpoints. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date, the algorithm in Appendix13.2 will be used.

10 STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

Descriptive statistics will be used to summarize disposition, demographics, baseline characteristics, baseline disease characteristics, study drug administration, efficacy and safety outcomes. Descriptive summaries of discrete data will present the sample size and the incidence as frequency and percentage. Descriptive summaries of continuous data will present the sample size, group mean, standard deviation, median, and range. Confidence intervals (CIs) may be included as appropriate.

10.2 Subject Accountability

The number of subjects enrolled by site will be presented. Subject disposition will be summarized for all enrolled subjects including the following information:

- Subject status on study drug
- Count and reason for study drug discontinuation
- Subject status on study
- Count and reason for study termination
- Time on study

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

10.4 Baseline Data

Summaries of demographics, baseline characteristics, and baseline disease characteristics will be presented for subjects in the All-treated Population.

10.4.1 Demographics

- Sex (Male, Female)
- Age (continuous)
- Age category (<65 versus ≥ 65, <75 versus ≥75)
- Ethnicity
- Race
- Region

10.4.2 Baseline Characteristics

- Height (cm)
- Weight (kg)
- ECOG performance status

10.4.3 Baseline Disease Characteristics

- Time (months) from initial diagnosis to first dose
- Tumor bulk (grouped as <5 cm, ≥5 and <10 cm, ≥10 cm)
- Tumor burden (cm^2)
- Ann Arbor staging for lymphoma
- Extranodal disease
- Bone marrow aspiration and biopsy result
- Simplified MIPI score (low risk, intermediate risk, high risk)
- Refractory disease (yes/no)
- Number of lines of prior therapies for MCL (continuous and grouped as 1, 2, ≥3)
- Lactate dehydrogenase (LDH) > upper limit normal (yes/no)

10.5 Treatment and Medications

10.5.1 Prior Anticancer Therapies

A prior anticancer therapy is defined as a systemic therapy subjects received, either as a single or combination therapy, for the treatment of active MCL with a start and end date occurring before the date of first dose of acalabrutinib. Therapies given as a consolidation or maintenance of a response or remission will not be considered as a separate regimen. Preparatory regimen and transplant will not be considered as separate regimens. Prior number of regimens for MCL is the total number of lines of therapy that a subject received for MCL before he/she entered this study. The number of lines and type of prior therapy for MCL will be summarized.

10.5.2 Prior and Concomitant Medications Received for Indications Other than MCL

Data reported on concomitant medications CRF page will be used. Medications started or ended prior to first dose will be considered as prior treatment. Concomitant therapy is defined as all medications used on or after the first dose, through the treatment phase, and for 30 days following the last dose of study drug. Using this definition, a medication can be classified as both prior and concomitant. The start date and end date will be imputed based on the rules provided in Section 9.1 of the SAP. Medications with completely missing start and stop dates will be considered as both prior and concomitant medications.

Prior and concomitant medications other than antineoplastic agents or other systemic therapies for MCL after enrollment will be summarized by the World Health Organization (WHO) Drug Dictionary therapeutic class, pharmacological class, and preferred term.

10.5.3 Subsequent Anticancer Therapy for MCL

Subsequent anticancer treatments for MCL are reported on the alternative cancer therapy CRF. Treatment started after discontinuation of acalabrutinib (i.e. started after the last dose of acalabrutinib) will be considered as subsequent anticancer treatment for MCL. The start date of first subsequent anticancer treatment will be considered as the start of subsequent anticancer therapy. Subject listing of subsequent anticancer therapy for MCL will be provided.

10.5.4 Exposure to Study Drug

Descriptive statistics (n, mean, standard deviation, median, and range) will be used to summarize:

- Duration of exposure (the interval between first dose date and last dose date)
- Actual cumulative dose (the total dose administered during the drug exposure period)
- Average daily dose (the ratio of total dose administered and treatment duration)
- Relative dose intensities (the ratio of the actual cumulative dose to the planned cumulative dose through the drug exposure period)

Dose withholding is defined as missing dose for ≥ 7 consecutive days. Dose reduction is defined as taking lower dose level (100 mg QD) for ≥ 3 consecutive days. Number of subjects with dose withholding and dose reduction will be summarized.

10.6 Analyses of Efficacy Endpoints

10.6.1 Primary Endpoint - Overall Response

10.6.1.1 Definition

ORR is defined as the proportion of subjects achieving either PR or CR as best overall response according to the Lugano classification as assessed by investigators.

10.6.1.2 Analysis Methods

The primary analysis of ORR will be conducted on the All-treated Population. ORR and the corresponding 95% two-sided CI calculated using the exact binomial distribution will be presented. Subgroup analysis per Section 6.2 will be provided.

The order of overall response category is: CR > PR > SD > PD. Descriptive statistics will be provided for best overall response. The number and proportion of subjects within each category of response as well as the associated 95% CIs will be presented. The proportion will be estimated by dividing the number of subjects within each category of response by the total number of subjects in the analysis population. Each subject will be counted within only one response group, with the best response during the study as the classification group.

10.6.2 Secondary Endpoints

10.6.2.1 Definition

10.6.2.1.1 Duration of Response

DOR is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of objective MCL disease progression or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date will be censored and the detail censoring rules for DOR are summarized in Appendix13.3.

10.6.2.1.2 Progression-free Survival

PFS is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of objective MCL disease progression or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date will be censored and the detail censoring rules for primary and sensitivity analyses of PFS are summarized Appendix 13.4.

10.6.2.1.3 Overall Survival

The duration of OS will be measured from the time of first study drug administration until the date of death from any cause. Subjects who are known to be alive as of their last known status will be censored at their last date known to be alive. The detail censoring rules for OS are summarized Appendix 13.5.

10.6.2.1.4 IRC-assessed Endpoints per Lugano Classification

ORR, DOR, and PFS assessed by the IRC per Lugano classification are defined similarly as those assessed by the investigator.

10.6.3 Analysis Methods

The analysis of DOR will be conducted on the subset of the All-treated Population who achieve CR or PR as their best overall response. The analysis of PFS and OS will be conducted on the All-treated Population. The analysis of DOR, PFS, and OS will be estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs will be calculated for event time quartiles, and event-free rates will be calculated at selected timepoints. In addition, the reason for censoring will be summarized for DOR, PFS, and OS. The same analysis methods for investigator-assessed ORR will be applied to IRC-assessed ORR. The discordant responses assessed by the investigator and IRC using the Lugano classification will be provided.

10.6.4 Exploratory Analyses

10.6.4.1 CCI

CCI [redacted]

[redacted]

[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

[redacted]

10.6.4.2 CCI [redacted]

[redacted]

(CCI [redacted]

10.6.4.3 CCI [redacted]

CCI [redacted]

10.7 Analyses Safety Endpoints

Safety analyses will be performed on the All-treated Population.

10.7.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA Version 19.1) will be used to code all AEs to a system organ class and a preferred term. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Study drug-related AEs are those assessed by investigator as related.

Treatment-emergent AEs are defined as those events that occur or worsen on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug.

Treatment-emergent AEs will be summarized by system organ class and preferred terms in descending order of frequency, by CTCAE toxicity grade. Drug-related treatment-emergent AEs, serious treatment-emergent AEs and drug-related serious treatment-emergent AEs, treatment-emergent AEs leading to treatment discontinuation, dose delay and dose modification will be summarized by preferred teams in descending order of frequency and by CTCAE toxicity grade.

Death information is reported in the study exit CRF for all deaths. Incidences of deaths are to be reported, along with the primary cause of death.

10.7.2 Adverse Events of Clinical Interest

Adverse events of clinical interest (ECI) corresponding search strategy are defined in Appendix B of the SAP for the acalabrutinib Integrated Summary of Safety (ISS).

Subject incidence rates of ECIs will be tabulated using the CTCAE Version 4.03.

10.7.3 Laboratory Test Results

Laboratory data of hematology, serum chemistry, serum immunoglobulin, and T/B/NK cell counts up to 30 days after last dose or the safety follow-up visit date, whichever is later, will be reported in SI units. Applicable laboratory results will be graded according to CTCAE Version 4.03. Generic normal ranges specified in American Medical Association (AMA) Manual of Style 10th Edition (2017) will be applied whenever reference ranges are not available.

Shift from baseline to the worst grade during the treatment will be provided as shift tables for selected parameters. Figures of selected parameters will be plotted overtime as appropriate.

10.7.3.1 Lymphocytosis

Lymphocytosis is defined as an elevation in absolute lymphocyte count (ALC) of ≥ 50% compared to baseline and a post-baseline assessment >5x10^9/L (Wang 2013). The number of subjects with at least one occurrence of lymphocytosis will be summarized. For subjects with lymphocytosis, resolution of lymphocytosis is defined as 1) a decrease of ALC value to the baseline level or lower, or 2) an achievement of ALC value that is below 5x10^9/L, whichever occurs first. Duration of lymphocytosis (DOL) is defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria.

DOL = Earliest date of meeting resolution criteria -Earliest date of meeting lymphocytosis criteria + 1.

Subjects who developed lymphocytosis but whose lymphocytosis was not resolved prior to the analysis cutoff date will be censored at the last sample date with non-missing ALC value at or prior to the analysis cutoff date.

Summary statistics will be provided for time to lymphocytosis. KM estimates for DOL will be provided.

10.7.3.2 Hepatitis B Test

Subjects with a history of hepatitis B virus (HBV) infection should be monitored monthly with a quantitative polymerase chain reaction (PCR) test for HBV DNA. Monthly monitoring should last until 12 months after last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Listing of subjects with any hepatitis B test will be provided.

10.7.4 Vital Signs

Summary statistics (mean, standard deviation, median, and range) will be produced for vital signs at baseline, maximum, change from baseline to maximum, last value, and change from baseline to last value.

To be included in the table, a subject must have both a baseline value and a value for the given post-baseline time point.

10.7.5 ECOG Performance Status

Change of ECOG from baseline to the maximum score during the treatment will be provided as shift tables.

10.7.6 Electrocardiogram

ECG data is collected at screening. The investigator assessment of clinical significance categorized as normal, abnormal but not clinically significant, and abnormal clinically significant will be summarized. The number of subjects with corrected QT interval (QTc) greater than 480 msec will also be provided. A listing of subject with abnormal and clinically significant baseline ECG results or QTc> 480 msec will be produced.

11 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There is no major change from protocol-specified analyses.

12 LITERATURE CITATIONS / REFERENCES

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13 APPENDICES

13.1 Definitions

13.1.1 Study day

The study day will be calculated in reference to the date of first dose date. Study Day 1 is defined as the date of first dose of acalabrutinib. For assessments that occur on or after first dose date, study day is defined as (date of assessment – date of first dose + 1). For assessments that occur prior to first dose date, study day is defined as (date of assessment – date of first dose). There is no Study Day 0.

13.1.2 Simplified MIPI Score

The simplified MIPI score will be derived based on baseline values of 4 prognostic factors: age, and ECOG, LDH, white blood cell (WBC). Points will be assigned to each of these factors as presented below and the score will be derived by adding the points for all 4 factors. A score of 0-3 indicates low risk, 4-5 indicates intermediate risk, and 6-11 indicates high risk (Hoster 2008).

Points	*Age (y)*	*ECOG*	*LDH ULN**	*WBC, 10^9/L*
0	<50	0-1	<0.67	<6.7
1	50-59	-	0.67-0.99	6.7-9.9
2	60-69	2-4	1.0-1.49	10.0-14.9
3	≥70	-	≥1.5	≥15.0

*LDH relative to upper limit of normal.

13.1.3 Refractory Disease

Refractory disease is defined as a lack of at least a partial response to the last therapy before study entry (Wang 2013). Refractory disease will be assessed based on the response to the last MCL treatment regimen a subject received prior to study entry and will be categorized as Yes, No. Subject without achieving at least PR or with unknown response to the last treatment regimen prior to study entry will have a value Yes.

13.1.4 Extranodal Disease and Bone Marrow Involvement at Baseline

The extra nodal sites of lymphoma data reported on ‘Disease History’ CRF will be used. Subjects with any sites/extra nodal notations box checked other than ‘None’, ‘Spleen’ or ‘Waldeyer's/Tonsil, Naso-oropharynx’ will be considered to have extranodal disease at baseline. The detail extranodal sites will be summarized in the baseline characteristics table.

Data reported on 'Bone Marrow Biopsy and Aspirate' CRF will be used to derive bone marrow involvement for subgroup analysis. Subjects with bone marrow biopsy and aspirate result box checked 'Not Involved' at baseline based on any method of assessment will be considered to have no bone marrow involved at baseline. Subjects with result box checked 'Involved', 'Indeterminant' or 'Other' will be considered to have bone marrow involvement as a conservative approach.

13.1.5 Gastrointestinal Disease at Baseline

Data reported on 'Disease History' CRF page will be used. Subjects with GI (gastrointestinal) box checked in the sites/extra nodal notations field will be considered to have gastrointestinal disease at baseline.

13.1.6 Tumor Bulk, Bulky Disease, and Tumor Burden at Baseline

Data reported on the CRF page lesion assessment will be used to derive these parameters.
Tumor bulk is defined as the largest diameter of a lymph node.
Tumor burden is defined as the sum of the product of diameters of all target lesions at baseline.

13.1.7 Adequate Disease Assessment

The adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred, as assessed by investigator. The adequate disease assessment should have response recorded other than 'Unknown/NA' in the 'Response Assessment' CRF page. Clinical assessment of PD without any objective evidence will not be considered as adequate disease assessment.

13.2 Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

If both month and day are missing for death date or a death date is totally missing, do not impute and censor the subject survival time.

13.3 Censoring Rules for Duration of Response

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented PD and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of Death	Death
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
No documented PD or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
No documented PD or death at the time of data cutoff and subject not received subsequent anticancer therapy or subsequent anticancer therapy started after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Withdrew consent without documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up without documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up

13.4 Censoring Rules for Progression-free Survival

13.4.1 Primary Analysis of PFS

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented PD and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of Death	Death
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
No documented PD or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
No documented PD or death at the time of data cutoff and subject not received subsequent anticancer therapy or subsequent anticancer therapy started after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Withdrew consent without documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up without documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up
No post-baseline adequate disease assessments	Censored	Date of first dose	No postbaseline adequate disease assessments
No baseline disease assessments	Censored	Date of first dose	No baseline disease assessment

13.4.2 Sensitivity Analysis of PFS

A sensitivity analysis will be performed where all PD or death (including those after the start of subsequent anticancer therapy) will be considered as events. The censoring rules for this analysis are summarized below.

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented between scheduled visits on or before data cutoff	Event	Earliest date of disease assessment documenting progression	PD
Death before first PD assessment or between adequate assessment visits on or before data cutoff	Event	Date of Death	Death
Withdrew consent without documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up without documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up
No documented PD or death at the time of data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
No postbaseline adequate disease assessments	Censored	Date of first dose	No postbaseline adequate disease assessments
No baseline disease assessments	Censored	Date of first dose	No baseline disease assessment

13.5 Censoring Rules for Overall Survival

Situation	Outcome	Date	Event Description/ Censoring Reason
Death on or before data cutoff	Event	Date of death	Death
Alive before data cutoff	Censored	Date subject last known to be alive	Alive on or before data cutoff
Death after data cutoff	Censored	Date of data cutoff	Alive on or before data cutoff
Alive on or after data cutoff	Censored	Date of data cutoff	Alive on or before data cutoff
Withdrew consent prior to data cutoff	Censored	Date of discontinuation from study participation as reported on study exit CRF	Withdrew consent
Lost to follow-up prior to data cutoff	Censored	Date subject last known to be alive	Lost to follow-up