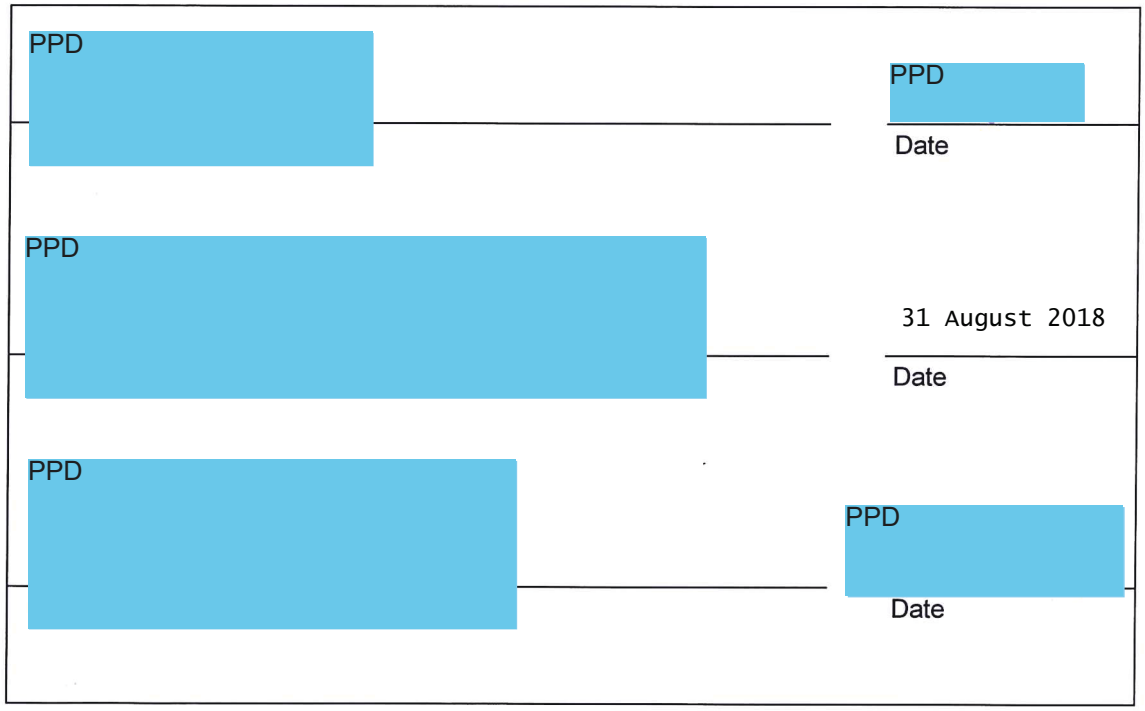
Protocol Number: ACE-LY-110

Protocol Title: A Phase 1/2 Proof-of-Concept Study of the Combination of Acalabrutinib and Vistusertib in Subjects with Relapsed/Refractory B-cell Malignancies

Version: 1.0

Version date: 16 Aug 2018

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



Statistical Analysis Plan

A Phase 1/2 Proof-of-Concept Study of the Combination of Acalabrutinib and Vistusertib in Subjects with Relapsed/Refractory B-cell Malignancies

Protocol Number: ACE-LY-110

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Study Statistician:	PPD

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TABLE OF ABBREVIATIONS

AE(s)	adverse event(s)
BID	twice per day (dosing)
CI	confidence interval
CR	complete response (remission)
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DRR	durable response rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
ICF	informed consent form
IPD	important protocol deviation
IXRK	Interactive Voice/Web Response System
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeter of mercury
mTOR	Mammalian target of rapamycin
MTD	maximum tolerated dose(s)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic, pharmacodynamics, or progressive disease
PFS	progression-free survival
PK	pharmacokinetic or pharmacokinetics
PO	orally
PR	partial response (remission)
PT	preferred terms
QD	once per day (dosing)
QTcF	QT interval corrected by Fridericia's formula
R/R	relapsed/refractory
RS	Richter syndrome
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SI	International System of Units
SMQ	Standardized MedDRA Queries
SOC	system organ class
SRC	Safety Review Committee

TEAE(s)	treatment emergent adverse event(s)
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol Amendment 2.0, 06 February 2018 for Study ACE-LY-110, which is entitled “A Phase 1/2 Proof-of-Concept Study of the Combination of Acalabrutinib and Vistusertib in Subjects with Relapsed/Refractory B-cell Malignancies.”

The scope of this plan includes the final analysis. Due to early closeout of the study at Part 1, the planned primary analysis as described in the protocol (after all ongoing subjects have had the opportunity to complete at least 3 scheduled post-baseline scans) will be considered the final analysis. The clinical study report (CSR) will be written. Any changes to the methods described in the final SAP will be documented in the CSR.

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

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

Part 1 Primary Objective

To determine a dose and schedule for vistusertib in combination with acalabrutinib 100 mg twice a day (bid) for evaluation in Part 2

Part 2 Primary Objectives

Under original protocol, the objective for Part 2 was to evaluate the safety of acalabrutinib and vistusertib when coadministered. Due to early closeout of the study at Part 1, no Part 2 objectives will be evaluated.

2.2 SECONDARY OBJECTIVES:

- To evaluate the PK of acalabrutinib and vistusertib when coadministered
- To evaluate the clinical activity of acalabrutinib and vistusertib, when coadministered, as measured by overall response rate (ORR), including complete response (CR) rate, duration of response (DOR), durable response rate (DRR), progression-free survival (PFS) and overall survival (OS)

2.3 EXPLORATORY OBJECTIVES

CCI [redacted]

- CCI [redacted]

[redacted]

3. STUDY OVERVIEW

3.1 Study Design

This proof-of-concept Phase 1/2, multicenter, open-label study was designed to evaluate the safety, PK, PD, and efficacy of acalabrutinib in combination with vistusertib in relapsed/refractory (R/R) subset of diffuse large B-cell lymphoma (DLBCL). Under the original protocol, the study was divided into 2 parts. Part 1 of the study was to evaluate the safety, PK, and PD of combining acalabrutinib 100 mg twice a day (BID and vistusertib (various doses and schedules). Part 1 was to be used to select the vistusertib dose and schedule for Part 2. The Part 2 portion of the study was to allow for expansion groups in select B-cell histologies to further evaluate safety, efficacy, and PKPD of the combination treatment of the selected dose regimen.

On 21 May 2018, a decision was made by sponsor stop enrollment and close this study (Target: vistusertib dose level 0). The primary reason was that inhibition of Torc-2 protein, which is a target of vistusertib, was not as strong as expected as determined by pharmacodynamic studies. In addition, PK data from subjects at vistusertib dose level 0 suggested that increasing the dose to level 1 would only increase exposure by approximately 20%, which is not expected to provide sufficient Torc-2 coverage to differentiate from approved Torc-1 inhibitors and could increase risk for toxicity.

Part 1

Part 1 of the study planned to include adult subjects with any of the following relapsed/refractory disease types:

- De novo DLBCL
- Transformed DLBCL
- Richter syndrome (RS)

Subjects were scheduled to take acalabrutinib BID at approximately 12-hour intervals. A treatment cycle was defined as 28 days. The acalabrutinib dose was 100 mg bid. Acalabrutinib is administered on every day of the 28-day cycle.

Although acalabrutinib monotherapy has not demonstrated dose-limiting toxicities (DLTs) to date, the safety of the combination of acalabrutinib and vistusertib in this patient population was assessed. Therefore, a safety analysis was planned when 6 subjects had been enrolled in each schedule (see below). Eligible subjects were randomized 1:1 to receive one of the following starting regimens of vistusertib through use of an Interactive Voice/Web Response System (IXRS):

Schedule 1 (continuous dosing): Vistusertib 35 mg bid continuous dosing (1 cycle = 28 days), n=6

--Or--

Schedule 2 (intermittent dosing): Vistusertib 100 mg bid intermittent dosing (2 days on/ 5 days off over the 28-day cycle), n=6

The following doses/schedules for vistusertib were planned to be evaluated in combination with acalabrutinib 100 mg bid in Part 1:

	Level -1 (Starting Dose)	**Level 0 (Target Level)**	**Level +1**
Continuous dosing schedule (**Schedule 1**)	35 mg bid (daily) n=6	50 mg bid (daily) n=6	75 mg bid (daily) n=6
Intermittent dosing schedule (**Schedule 2**)	100 mg bid (2 days on/ 5 days off) n=6	125 mg bid (2 days on/ 5 days off) n=6	150 mg bid (2 days on/5 days off) n=6

Abbreviations: bid = twice per day

Standard DLT criteria were used to assess safety during the first cycle of treatment of the combination treatment. (To be evaluable for DLT, patients who have not experienced DLT must have received at least 75% of scheduled doses. Patients who have experienced DLT do not have a minimum dosing requirement.) Each schedule was independently assessed. Escalation to the target level could occur until the DLT review had occurred. If ≤1 DLTs occurred during Cycle 1 in the 6 subjects enrolled in a given schedule, then the dose of vistusertib was escalated as per study schema in the protocol and 6 new subjects were enrolled and assessed for DLT. Detailed information on DLT review and toxicity monitoring was provided in Section 3.7 and Section 3.14 of the study protocol.

Since the study will not proceed to Part 2, the final analysis will be conducted after all ongoing subjects in Part 1 have had the opportunity to complete at least 3 scheduled post-baseline scans.

3.2 Sample Size

Under current protocol (version 2.0), the sample size for Part 1 and Part 2 were set up separately. Depending on dose escalation/de-escalation and enrollment in the expansion groups, up to 71 subjects were planned to be enrolled in this study:

- Part 1: ≤36 subjects
- Part 2: ≤35 subjects

In Part 1 (dose selection), enrollment of 6 subjects per dose level limited the number of subjects exposed, consistent with the expected safety profiles of the study drugs, but included sufficient number of subjects to explore effects on PD biomarkers of BTK and mTOR inhibition. The trial employed the standard NCI definition of MTD (dose associated with DLT in <33.3% of subjects assessed during Cycle 1). In Part 1, subjects who did not meet the DLT review criteria were replaced.

By the time of the decision of study closeout, two dose levels (level -1 and level 0) had been explored in each of the two schedules (continuous/intermittent vistusertib dosing), resulting in enrolling 24 patients. In the cohort of dose level -1 35 mg BID continuous, one subject who was not DLT evaluable was replaced. Therefore, the overall number of subjects is 25.

3.3 STUDY ENDPOINTS

3.3.1 Primary Endpoints

- The safety endpoints are the primary endpoints of this study, including type, frequency, severity, and relationship to either or both study drug of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious adverse events (SAEs), AEs leading to dose modification, dose delay, and discontinuation of any study drug.

3.3.2 Secondary Endpoints

- PK Endpoints
- Efficacy Endpoints
    - ORR (CR + PR)
    - DRR
    - CR rate
    - DOR
    - PFS
    - OS

4. HYPOTHESES AND MULTIPLICITY

No formal statistical hypotheses will be tested and no multiplicity adjustments will be made. This proof-of-concept study will assess the clinical potential of acalabrutinib in combination with vistusertib in relapsed/refractory subsets of B-cell malignancies.

5. ANALYSIS SETS

The following definitions will be used for the safety and efficacy analysis populations.

5.1 Safety Analysis Set

The safety analysis set includes all subjects who received at least one dose of any study drug (either acalabrutinib or vistusertib). The safety analysis set will be used for evaluating the safety endpoints.

5.2 Efficacy Evaluable Analysis Set

The efficacy evaluable analysis set includes all subjects in the safety analysis set with a baseline tumor assessment. The efficacy analysis set will be used for evaluating the efficacy endpoints, with the exception of DOR. The analyses of DOR will be conducted

on the subset of the efficacy evaluable analysis set who achieve CR or PR as their best overall response.

5.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set includes all subjects in the safety analysis set with evaluable PK parameters. Pharmacokinetic evaluable analysis set will be defined by PK/PD group.

6. SUBGROUP ANALYSIS

No subgroup analyses will be performed.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

Interim analysis was planned for Part 2 of this study. Because of the closeout of this study at Part 1, no interim analysis will be performed.

8. ANALYSIS TIMEPOINT AND CLINICAL STUDY REPORT

Due to early closeout of the study at Part 1, the planned primary analysis (after all ongoing subjects have had the opportunity to complete at least 3 scheduled post-baseline scans) will be considered as the final analysis. The clinical study report will be written.

9. MISSING VALUES

No imputation of values for missing data will be performed except for missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. The details of imputation rules for partial or missing dates are listed in Appendix 13.2.

10. STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

Descriptive statistics (including means, standard deviations, medians, minimum and maximum for continuous variables, and frequency, proportions, and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate.

Calculation of time to event or duration of event endpoints will be based on the study day of the event or censoring date rather than visit number or visit label. Missing efficacy or safety data will not be imputed unless otherwise specified.

The following rules will be used for the days to months/years conversion:

- 1 month= 30.4375 days;
- 1 year= 365.25 days.

All summaries will be presented by treatment group.

10.2 Subject Accountability

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

- Proportion of subjects who received study drug
- Proportion of subjects with study drug discontinuation and primary reason for study drug discontinuation
- Proportion of subjects discontinuing study and reasons for study discontinuation
- 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. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

10.4 Demographic and Baseline Characteristics

Summaries of demographic characteristics will be presented for age, age category (< 65, ≥ 65), sex, race, ethnicity, and geographic region for each study.

Baseline characteristics will be presented for Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, and number of prior anticancer therapies for each study.

10.5 Treatment and Medications

10.5.1 Prior Anticancer Therapies

Summary statistics will be presented for prior anticancer regimens (might include multiple therapies) and prior cancer-related surgery for each study. Prior cancer therapy categories will be adjudicated by the medical monitor.

10.5.2 Concomitant Medications

Concomitant medications will be coded and tabulated according to the World Health Organization Drug Dictionary (WHODRUG).

10.5.3 Exposure to Investigational Product

The number of subjects who received at least one dose of acalabrutinib, vistusertib, or both; duration of exposure; average daily dose of acalabrutinib; average weekly dose of vistusertib and relative dose intensity will be summarized for each investigational product and by treatment group.

Exposure parameters are defined in more detail in Appendix 13.1.

10.6 Safety Analyses

The safety analysis will be performed using the safety analysis set.

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA v20.1 or higher) 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 5. Study drug-related AEs are those assessed by investigator as related.

All AE tables will be summarized by treatment cohorts.

TEAEs 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 any study treatment.

TEAEs will be summarized by system organ class (SOC) and preferred terms in descending order of frequency, by CTCAE toxicity grade. Drug-related TEAEs, serious TEAEs, TEAEs leading to dose modifications, dose delay, and study treatment discontinuation will be summarized by preferred teams in descending order of frequency, by CTCAE toxicity grade.

Death information is reported in the death report form (CRF) for all deaths. Incidences of deaths are to be reported, along with the primary cause of death.

10.6.2 Laboratory Test Results

Laboratory data up to 30 days after last dose or the safety follow-up visit date, whichever is later, will be reported in International System of Units (SI) units. Applicable laboratory results will be graded according to CTCAE Version 5. For each laboratory parameter, the baseline laboratory value/grade is defined as the last laboratory value/grade collected on or prior to the date of the first dose of study

drug. Treatment-emergent laboratory abnormalities for selected parameters will be summarized.

10.6.3 Vital Signs

Body temperature (C), pulse (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), oxygen saturation (%), height (cm), and weight (kg) will be collected as scheduled in the protocol. For each parameter, summary statistics (mean, standard deviation, median, and range) will be produced for baseline, maximum, and minimum value.

10.6.4 ECOG Performance Status

ECOG performance status scores will be summarized for each treatment group using a shift table. The shifts in scores from baseline to worst ECOG score on treatment will be summarized.

10.6.5 12-Lead Electrocardiogram

The summary statistics (mean, standard deviation, median, and range) of QTc based on Fridericia's formula (QTcF) at baseline and each assessed time point will be produced. If triplicate ECGs were performed (at screening and Cycle 6 only, or if clinically indicated), the results will be summarized using the mean of the three measurements.

10.7 Efficacy Analyses

The efficacy analysis will be performed using the efficacy evaluable analysis set, with the exception of DOR. The analyses of DOR will be conducted on the subset of the efficacy evaluable analysis set who achieve CR or PR as their best overall response.

10.7.1 Overall Response Rate and Complete Response Rate

The ORR is defined as the rate of subjects who achieve either a PR or CR, according to the revised response criteria for malignant lymphoma (Cheson et al. 2014), as assessed by investigators, before receiving any other anticancer therapy. The corresponding 95% two-sided CIs with use of the exact binomial distribution will be calculated for ORR and CR rate.

10.7.2 Progression-Free Survival

PFS is defined as the time from first dose date to documented disease progression or death from any cause, whichever occurs first. Disease progression is determined by the investigators according to the revised response criteria for malignant lymphoma (Cheson

et al. 2014). Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median).

Data from surviving, non-progressing subjects will be censored at the date of the last adequate disease assessment that is on or before the start date of subsequent therapy. Data from subjects who have disease progression or die after more than one missed visit will be censored at the last visit date prior to the missing assessments that lack objective disease assessment. The details of definition of progression events and censoring rules are listed in Section 14.1.

Study treatment end date will be used as the date of progression for subjects who discontinued study treatment due to disease progression or death prior to their first disease assessment. Data for subjects who discontinued study treatment prior to their first disease assessment due to reasons other than disease progression or death will be censored at their study treatment start date.

10.7.3 Duration of Response

DOR is defined as the time from the first objective response of CR or PR to the time of documented disease progression or death due to any cause, whichever occurs first. Kaplan-Meier methods will be used if appropriate to estimate the event-free curves and corresponding quantiles (including the median). In case of very limited number of responders, the listing with duration of response and indicator of censoring might be used.
Data from surviving, non-progressing subjects will be censored at the date of the last adequate disease assessment that is on or before the start date of subsequent therapy. Data from subjects who have disease progression or die after more than one missed visit will be censored at the last visit date before the missing assessments that lack objective disease assessment. The details of definition of progression events and censoring rules are the same as for PFS endpoint and are listed in Section 14.1.

10.7.4 Durable Response Rate

The DRR is defined as the percentage of subjects who have a CR or PR lasting ≥8 weeks. This measure was intended mainly for study Part 2 of the analysis and will not be summarized since study was terminated at Part 1.

10.7.5 Overall Survival

Overall survival is defined as the time from treatment start date until date of death due to any cause. Since we are closing the study early, subjects will not be followed for survival after the last subject last visit for Part 1. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Kaplan-Meier methods will be used to estimate the survival curves and corresponding quantiles (including the median). Censoring rules are defined in more detail in Section 14.2.

10.8 Pharmacokinetic Analyses

A separate PK and/or PD analysis plan will be provided since those analyses will be performed by the vendor.

11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

The changes from protocol-specified analyses due to early closeout of the study at Part 1 as follows:

- Part 2 of the study was not conducted.
- The planned primary analysis as described in the protocol (after all ongoing subjects have had the opportunity to complete at least 3 scheduled post-baseline scans) is the final analysis.
- Subjects will not be followed for survival after the last subject last visit for Part 1.
- The DRR analysis was intended for Part 2 of the study and will not be summarized.

12. LITERATURE CITATIONS/REFERENCES

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3067.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, USDHHS, NIH, NCI; publish date November 27, 2017.

13. APPENDICES

13.1 Definitions

Study Day

The study day will be calculated in reference to the first dose date of study drug. Study Day 1 is defined as the first dose date of study drug. For assessments that occur on or

after the first dose date of study drug, study day is defined as (date of assessment – first dose date of study drug + 1). For assessments that occur prior to the first dose date of study drug, study day is defined as (date of assessment – first dose date of study drug). There is no Study Day 0.

Duration of Exposure

The duration of exposure to acalabrutinib or vistusertib will be calculated in months as (last dose date - first dose date + 1) / 30.4375. The gaps in treatment will be included. The duration of exposure in days will be used for planned dose calculation.

Total Dose

Total dose received is a sum of all actual doses taken through the treatment duration and will be presented in grams. For scheduled drug administration visits that are skipped, the actual dose will be 0.

Average Daily Dose (Acalabrutinib)

Average daily dose is total dose divided by duration of exposure in days.

Average Weekly Dose (Vistusertib)

Average weekly dose is total dose divided by number of weeks for vistusertib study treatment.

Relative Dose Intensity

Relative dose intensity is the ratio of total dose to the protocol-specified total dose through the duration of exposure.

13.2 Imputation Rules for Partial or Missing Dates

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, then date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, then 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 but before the first dose date, then the first dose date will be used; 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 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, then the death date will be used; if the imputed AE end date is before the AE start date, then the AE start date will be used.

Every effort will be made to obtain complete dates for deaths. If both month and day are missing for death date or a death date is totally missing, it will not be imputed; the subject survival time will be censored. If death year and month are available but day is missing, the following algorithm will be used:

- 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.

14. DETAILED CENSORING RULES FOR EFFICACY ENDPOINTS

14.1 PFS Events and Censoring Rules

Situation	PFS	
	Date of Progression or Censoring	Outcome
Progression documented on scheduled visit	Date of scheduled visit	Progression
Progression documented between scheduled visits	Date of unscheduled visit	Progression
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censor
Death before first PD assessment	Date of death	Progression

Death between adequate assessment visits	Date of death	Progression
Death or progression after only one missed visit	Date of death	Progression
Death or progression after 2 or more missed visits	Date of last visit with adequate assessment	Censor
Death or progression after 2 or more missed visits and only baseline disease assessment available	Date of 1st dose of study drug	Censor
No baseline disease assessments	Date of 1st dose of study drug	Censor
Baseline disease assessments only and no evidence of documented PD, treatment discontinuation due to PD or death within no more than one missed visit	Date of 1st dose of study drug	Censor
No progression	Date of last visit with adequate assessment	Censor
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censor
Subsequent anticancer treatment started	Date of last visit with adequate assessment	Censor

14.2 Overall Survival Censoring Rules

Situation	**Date Death or Censoring**	**Outcome**
Death at any timepoint	Date of death	Death
Lost to follow-up immediately after 1st dose of study drug	Date of 1st dose study drug	Censored
Not known to have died at or after the analysis cutoff date	The date last known alive before data analysis cutoff	Censored
Known to have died after the analysis cutoff date	Date of data analysis cutoff	Censored