DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-5013-CLL-009

A Phase 2, Multi-Center, Randomized, Double-Blind, Parallel-Group Study Of The Safety And Efficacy Of Different Lenalidomide (Revlimid®) Dose Regimens In Subjects With Relapsed Or Refractory B-Cell Chronic Lymphocytic Leukemia

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STATISTICAL ANALYSIS PLAN

A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP STUDY OF THE SAFETY AND EFFICACY OF DIFFERENT LENALIDOMIDE (REVLIMID®) DOSE REGIMENS IN SUBJECTS WITH RELAPSED OR REFRACTORY B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA

STUDY DRUG: CC-5013

PROTOCOL NUMBER: CLL-009

DATE FINAL: NOV 01, 2012

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SAP APPROVAL SIGNATURE PAGE	
INVESTIGATIONAL PRODUCT	CC-5013
SAP TITLE	A Phase 2, Multi-Center, Randomized, Double-Blind, Parallel-Group Study Of The Safety And Efficacy Of Different Lenalidomide (Revlimid®) Dose Regimens In Subjects With Relapsed Or Refractory B-Cell Chronic Lymphocytic Leukemia
SAP VERSION, DATE	Version 1.0 01NOV2012
SAP AUTHOR	Printed Name and Title / Signature and Date
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this Statistical Analysis Plan (SAP) and find its contents to be acceptable.
Statistical Therapeutic Area Head	
Signature	
Printed Name	
Clinical Therapeutic Area Head	
Signature	
Printed Name	
Lead Clinical Research Scientist	
Signature	
Printed Name	
Trials Safety Surveillance Head *(for safety portion only)*	
Signature	
Printed Name	

2. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ANOVA/ANCOVA	Analysis of Variance/Covariance
AST (SGOT)	Asparate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomic Therapeutic Chemical
CI	Confidence Interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRi	Complete response with incomplete bone marrow recovery
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFS	Event-free survival
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FDA	Food and Drug Administration
FISH	Fluorescence in Situ Hybridization
HRQL	Human Related Quality of Life
ITT	Intent to Treat
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease

Abbreviation or Specialist Term	Explanation
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation or Specialist Term	Explanation
nPR	Nodular partial response
OS	Overall Survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial Response
SAE	Serious adverse event
SD	Stable disease
SOC	System Organ Class
TTP	Time to progression
USA	United States of America
WHO	World Health Organization
ZAP 70	Zeta-Chain-Associated Protein Kinase

3. INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for protocol CC-5013-CLL-009 "A Phase 2, Multi-Center, Randomized, Double-Blind, Parallel-Group Study of The Safety and Efficacy of Different Lenalidomide (Revlimid®) Dose Regimens in Subjects with Relapsed or Refractory B-Cell Chronic Lymphocytic Leukemia".

Subjects were randomized (1:1:1) in a double-blind fashion to the 5 mg, 10 mg, and 15 mg starting dose arms (treatment arm 1, treatment arm 2, and treatment arm 3 respectively).

The randomization procedure was accomplished by a validated interactive voice response system (IVRS). Subjects were stratified at randomization by (i) relapsed vs refractory to their last purine-analog or bendamustine based treatment regimen (if subject has received both, the status post most recent purine-analog or bendamustine regimen was used for stratification) and (ii) age < 65 years of age vs ≥ 65 years of age. The subjects received lenalidomide once daily in a 28 day cycle and will be escalated every 28 days as tolerated in a stepwise manner up to a maximum of 25 mg daily.

Depending on the starting dose, subjects were allocated in a double-blind fashion to three different regimens and will escalate every 28 days, based on individual subject tolerability, as follows:

- Treatment Arm 1: 5 mg →10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 2: 10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 3: 15 mg →20 mg →25 mg/daily

The primary objective of this study was to evaluate the safety of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL). The secondary objective was to evaluate the efficacy of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell CLL.

This study was conducted using a randomized Bayesian schedule-administration design that jointly models toxicity/disease progression outcomes using an extension method. The object of interest was to determine if a particular treatment administration schedule is superior to other competing schedules. No treatment arm was stopped during the conduct of the study.

In total 104 subjects were enrolled into the study.

In August 2012, a decision was made to deviate from the randomization procedure and enroll the last subject into the 10mg cohort in order to have at least 6 valid (with sufficient PK samples) subjects in each starting dose level into the PK sub-study of the trial.

Per the Monitoring Committee (DMC) meeting on 10 May 2012, a unanimous decision was made to unblind the study in December 2012.

This statistical analysis plan (SAP) provides a comprehensive and detailed description of the rationale and statistical techniques to be used to achieve the objectives of the study. It specifies the pre-planned analysis in the study protocol, and provides additional details concerning the planned and exploratory analyses that will be conducted for all the data collected during the study and in the follow-up phase. The SAP will be finalized and approved prior to the clinical database lock for the planned analysis on progression-free survival (PFS), and updated for overall survival (OS) analyses as appropriate.

All statistical analyses will be conducted using SAS® Version 9.1 or higher.

4. OBJECTIVES

Primary

To evaluate the safety of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell CLL.

Secondary:

To evaluate the efficacy of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell CLL.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan

CC-5013-CLL-009 is a phase 2, multicenter, randomized, double-blind, parallel-group adaptive design study that will evaluate the safety and efficacy of different lenalidomide dose regimens administered orally in subjects with relapsed or refractory B-Cell Chronic Lymphocytic Leukemia. All regimens use an intra-subject stepwise dose escalation scheme with three different initial ascending starting dose of 5 mg daily, 10 mg daily, or 15 mg daily and then escalating in a stepwise manner every 28 days to reach a maximum dose of 25 mg daily based on subject tolerability. Approximately 105 subjects will be enrolled, 35 subjects per arm.

5.1.1. Adaptive Study Design

The CC-5013-CLL-009 phase 2 study will compare different treatment regimens (starting dose of 5 mg, 10 mg, or 15 mg daily, followed by an intra-subject escalation up to a maximum of 25 mg daily) using a Bayesian approach to evaluate both efficacy and toxicity. This adaptive design will consider joint efficacy (progression rate) and toxicity outcomes to stop randomization of less promising arms (Bekele, 2008b). At any time accrual to a starting dose arm will be stopped if unacceptable toxicities are observed in that arm.

5.1.2. Duration of Treatment

Subjects will receive study drug until PD or unacceptable toxicity develops. The continuation of lenalidomide treatment duration until disease progression is supported by Chanan-Khan and Ferrajoli studies which report that subjects with relapsed CLL that have received lenalidomide therapy for more than one year continue to improve their response to treatment (Chanan-Khan, 2006a) (Chanan Khan, 2007) (Ferrajoli, 2008). In the Chanan-Khan study the median time to best response was 5.9 months (range 1.6 to 18.3 months). In the Ferrajoli study time to best response was 6 months in 11 subjects and 9 months in 3 subjects.

5.1.3. Safety

Subjects will be evaluated for AEs at each visit with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 3.0) used as a guide for the grading of severity with the exceptions of hematological toxicities and TLS. Hematological toxicities will be graded as specified in the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008). Tumor lysis syndromes will be graded as specified by the Cairo-Bishop grading system.

Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events (AEs) throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events (SAEs) regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the survival follow up period. Subjects will be followed until 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later.

5.1.4. Efficacy

Tumor response will be assessed according to the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008), including complete response (CR),CR with incomplete bone marrow recovery (Cri), nodular partial response (nPR), partial response (PR), stable disease (SD), and PD. Evaluation of response will be performed after 3 cycles of therapy and every 4 weeks thereafter.

For those subjects who reach PR, CRi or CR, a CT scan of the neck, chest, abdomen and pelvis to assess lymphadenopathies will be performed at the PR and CR/CRi confirmation visits (≥8 weeks to ≤ 12 weeks after all clinical and laboratory response criteria have been met for PR or CR/CRi). Those subjects whose response was down-graded based on the CT scan interpretation at the PR or CR/CRi confirmation visit will have the CT scan repeated 4 months later at the location where remaining disease has been documented, as long as clinical and laboratory response remains present to try to document further improvement.

For those subjects who reach CR or CRi, a bone marrow aspirate and bone marrow biopsy will be performed at the CR/CRi confirmation visit (≥ 8 weeks to ≤ 12 weeks after all clinical and laboratory response criteria have been met). If the bone marrow is hypocellular, a repeat specimen should be obtained after 4 weeks, provided that the blood counts have recovered. If the bone marrow biopsy shows disease involvement (30% or greater lymphocytes, or nodules positive for B-CLL cells by immunohistochemistry), an additional bone marrow biopsy and aspirate will be taken 4 months later as long as clinical and laboratory response remain to document further improvement.

Minimal residual disease (MRD) will be evaluated for those subjects who reach CR or CRi. A peripheral blood and bone marrow aspirate sample will be collected for MRD analysis by flow cytometry at the CR/CRi confirmation visit.

- If peripheral blood and bone marrow are both MRD-positive, peripheral blood samples will be repeated and assessed up to 3 additional times at 8 week intervals to try to document MRD negativity in subjects who reach confirmed CR or CRi (see Follow-up MRD assessments).
- If peripheral blood is MRD-negative and bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
- If both the peripheral blood and bone marrow are MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug.

Follow-up MRD assessments:

- If any of the repeat peripheral blood assessments indicate MRD-negativity, a bone marrow aspirate sample should be collected and retested as soon as possible to confirm MRD negativity.

- If the bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
- If at any time, the bone marrow is MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug.

5.1.5. Exploratory Assessments

The following exploratory assessments will be performed in consented subjects:

- Blood samples for zeta-chain-associated protein kinase (ZAP-70), V_H mutational status /TP53 mutation analysis, fluorescence in situ hybridization (FISH) studies for cytogenetic assessment, and disease confirmation by immunophenotyping will be collected at baseline.

Subjects will complete quality of life questionnaire (FACT-Leu and EQ-5D questionnaires) at time points detailed in **Error! Reference source not found.** of the protocol.

5.1.6. Pharmacokinetic assessments

Pharmacokinetic assessments will be performed in up to 40 subjects who provide consent at select centers. Following the enrollment of 90 subjects, participation in the PK sub-study will be mandatory for all additional subjects enrolled. PK Subjects will undergo intensive and sparse PK sampling as detailed in **Error! Reference source not found.** of the protocol

5.2. Study Endpoints

Primary

- Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to lenalidomide]

Secondary

- Response rate; International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines for the diagnosis and treatment of CLL (Hallek, 2008)
- Duration of response
- Time to response (TTR)
- Time to progression (TTP)
- Event-free survival (EFS)
- Progression-free survival (PFS)
- Overall survival (OS)

Exploratory

- Evaluation of response rate in predefined biologic risk group
-
- Investigate the relationship between pharmacokinetics (PK) and response (biomarkers or clinical outcomes as appropriate)
- Quality of Life

For all the efficacy endpoints, the determination of responses (including progression of disease) is based on the Independent Response Adjudication Committee (IRAC) review of the CLL response data using IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008).

5.3. Data and Analysis Quality Assurance

This protocol is conducted under the sponsorship of Celgene Corporation. The data collection and management will be performed according to the Celgene Standard Operating Procedures (SOP). The quality of the analyses will be verified through a programming validation process. At a minimum, all tables of key efficacy and safety variables will be validated based on an independent programming of these results.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Sample Size

The sample size will be approximately 105 subjects, 35 per arm, barring early stopping. The original accrual rate is assumed to increase with time such that approximately 9-12 subjects will accrue in the first 3 months and a total of 41 to 55 subjects will accrue by 6 months with the remainder accruing by 60 weeks. Therefore, in addition to monitoring toxicity and progression, the accrual rate will be monitored.

The operating characteristics for the Bayesian Beta prior/schedule-administration adaptive design are given in protocol **Error! Reference source not found.**.

6.2. Randomization and Stratification

Stratification and randomization will be performed by IVRS, an Interactive Voice Response System, to ensure a 1:1:1 central randomization. Subjects will be stratified at randomization by:

- Relapsed versus refractory to their last purine-analog or bendamustine based treatment regimen [relapsed/refractory as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008). If a subject has had prior purine-analog based and bendamustine based regimen, the stratification will be based on the subject's status post most recent regimen.
- Age < 65 years of age versus ≥ 65 years of age

6.3. Randomized Bayesian Design

This study will be conducted using a randomized Bayesian schedule-administration design that jointly models toxicity/response outcomes using an extension methods developed in (Bekele, 2004) (Bekele, 2005) (Bekele, 2008a) (Bekele, 2008b). Schedule-administration (or treatment strategy) designs differ from standard treatment designs in that the object of interest is not to determine if one treatment is superior to an alternative treatment, but to determine if a particular treatment administration schedule is superior to other competing schedules. In the context of the current design Celgene is interested in evaluating whether various intra-subject dose-escalation schemes are safe and effective while monitoring safety and efficacy (futility). Specifically, while treatment starts at various doses ranging from 5 mg/daily to 15 mg/daily, the goal is to perform intra-subject dose escalation (every 28 days as tolerated) until a maximum dose of 25 mg/daily is achieved. The decision to escalate is based on how well the subject tolerates the lower dose levels. While these dose escalations are taking place, toxicity and the progression rate will be monitored.

Operationally, the study will proceed as follows: Subjects will be randomized to one of the three treatment arms. The first interim analysis (toxicity only) will be performed once 18 subjects have completed one 28-day cycle. Subsequent interim analyses will occur at 13-week intervals to monitor both combined toxicity and progression rates.

If a treatment arm is dropped then all new subjects will be randomized equally into the remaining arms.

6.4. Analysis Populations

6.4.1. Safety Population

The safety population is defined as all randomized subjects who receive at least 1 dose of the study drug.

Drug exposure and all safety analyses (including adverse events, labs, and deaths) will be based on the safety population. Subjects will be analyzed according to the initial treatment actually received.

6.4.2. Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population is defined as all subjects who are randomized, independent of whether they received study drug or not. The ITT population will be used for the efficacy analysis.

Subject disposition, demographics, baseline characteristics, and all efficacy analyses will be based on the ITT population unless specified otherwise. All subjects in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

6.5. Reporting Conventions

The algorithms, imputations, and conventions that will generally apply to programmed manipulations of the data for summary tabulations and individual subject data listings are described in this section.

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the:

- Program source (e.g, SAS program name, including the path, that generates the output) and
- Data extraction date (e.g, the database lock date).

The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also appear on each output page and will indicate the date the output was generated by the analysis program.

6.5.1. Tables

Data in tables will be summarized for each of the treatment arms and overall subjects when appropriate. Tables will contain the number of subjects in the analysis population for each column and the total number. Presentations will be summarized by cycle if applicable. In selected presentations the event or assessment indicating the most severe event by NCI CTCAE

toxicity grade or most abnormal assessment (analysis of the "worst" case) for each subject over the course of the study will be summarized.

Time points in the summaries will reflect the time periods described in the protocol and CRF, such as 'Baseline', 'Cycle 1 Day 1', 'Cycle 2 Day 1', etc.

Age will be displayed in years and relative days (e.g., study days) will be displayed in days. Dosing exposure and treatment durations will also be displayed in days; all other time intervals will be presented in weeks.

The following descriptive statistics will be displayed for each quantitative variable: n, mean, median, standard deviation (SDev), minimum, and maximum.

Qualitative variables will be presented as category frequencies and percentages. The denominator for calculating percentages will be either the number of subjects in the analysis population or the number of non-missing observations in the treatment arm for the particular variable presented. Visit windows will not be used in the data analyses. The cycle number recorded on the CRF, if available, will be used to mark the data collection time points. Actual visit or assessment dates will be used to calculate intervals of time.

If a given table template specifies the summarization of a given qualitative CRF variable and no such response appears on a CRF for any of the subjects in the study population appropriate to that table, the entire row may be deleted from the summary rather than present a row of zeroes for that response.

6.5.2. Listings

Data listings will be sorted by treatment arm (for unblinded analysis), subject number, and cycle number, if applicable.

6.5.3. Dates

Dates will be displayed in ddmmmyyyy format (e.g., 30JUN2002).

Calculations using dates will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication (e.g, lenalidomide) plus 1 day. The generalized calculation algorithm for relative day: STUDY DAY = [(TARGET DATE – DSTART) + 1 where DSTART = the start day of study drug]. Note that Study Day 1 is the first day of treatment of study drug. For study days before the start day of study drug the algorithm is: STUDY DAY = (TARGET DATE – DSTART). Negative study days are reflective of observations obtained during the baseline/screening period.
- Age (expressed in days) is calculated: AGE = Informed Consent Date – DTBIRTH + 1. In practice, age will be converted to years by dividing the difference by 365.25 days, then truncating to a whole number.
- The conversion between weeks and months can be performed by using the following conversion formula (without truncation):
  MONTHS = WEEKS *7/30.4.

- Partial dates will be reported as recorded in the data listings. There will be no imputation for missing parts of dates, unless for the purpose of
    1. determining treatment emergent AEs when the AE start date is partial, or
    2. differentiating medication taken prior to the study treatment from concomitant medication taken during the study when the medication start date is partial.

The conventions for imputing partial dates for such purposes are as follows:

1. The onset date has year but both month and day missing
    - If the year of onset = year of first study drug dose, then the onset date = First study drug dose date.
    - If the year of onset < year of first study drug dose, then the onset month = 12 and the onset day=last day of the month.
    - If the year of onset > year of first study drug dose, then the onset month = 1 and the onset day=1.

2. The onset date has year and month but day missing
    - If the year and month of onset = year and month of first study drug dose, then the onset date = first study drug dose date.
    - If the year of onset < year of first study drug dose, or the year of onset = year of first study drug dose but the month of onset < the month of first study drug dose, then the onset day = last day of the month.
    - If the year of onset > year of first study drug dose, or the year of onset = year of first study drug dose but the month of onset > month of first study drug dose, then the onset day = first day of the month.

7. SUBJECT DISPOSITION

For all subjects randomized, subject disposition will be summarized. Subject disposition includes the number of subjects in the following categories:

- ITT Population
- Safety Population

Reasons for treatment termination will be collected on the CRF and will be summarized for all randomized subjects with the following categories:

- Adverse events
- Disease progression
- Withdrew consent
- Death
- Lost to follow-up
- Protocol violation
- Other

A separate listing will be provided for subjects who did not receive at least one dose of study drug.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subjects' age, weight, and other continuous demographic and baseline variables including disease characteristics and prior treatments (Number of prior regimens Purine-analog refractory in any prior treatment line, percentage of subjects that received purine-analog treatment, bendamustine treatment or both in a line prior to study entry) will be summarized using descriptive statistics (e.g., mean, standard deviation, median, minimum and maximum), while the response to previous CLL treatment, race and other categorical variables will be summarized with frequency tabulations for each treatment arm separately and pooled over all treatment arms. Cytogenetic abnormalities will be identified and summarized by treatment arm.

Summaries for the demographics and baseline characteristics will be provided for the ITT population and safety population separately. Individual subject listings will be provided.

Medical history data will be summarized using frequency tabulations for each treatment arm by system organ class and preferred term separately and pooled over all arms using the safety population.

9. DRUG EXPOSURE

The following measures of drug exposure will be analyzed for all three treatment arms.

Treatment Duration

The first dose date of lenalidomide is considered the start date of the study treatment. For each cycle, the lenalidomide start date will be considered the cycle start date and the day before that (after the 1st cycle) will be considered the end day of the previous cycle. The end date of the last cycle will be calculated as the start date of last treatment cycle plus 27 days, unless subject discontinues study or dies before the end of the last cycle, in which case the end date of the last cycle will be the treatment discontinuation date or the death date.

For each treatment arm, the treatment duration will also be calculated, and defined as:

[(The end of the last cycle of the study drug) – (the first dose date of the study drug)+1]

Cumulative Dose

Cumulative dose will be calculated for each lenalidomide arm. The cumulative dose is defined as the sum of all doses taken across the treatment period (in milligrams).

Dose Exposure

Dose exposure will be calculated for each lenalidomide arm. Dose exposure is defined as the total number of days on the study drug during the treatment phase (excluding the periods of dose interruptions per protocol).

Average Daily Dose

Average dose will be calculated for each lenalidomide arm. Average daily dose is defined as the cumulative dose divided by dose exposure (mg/day).

Dose Intensity

Dose intensity will be calculated for each lenalidomide arm. Dose intensity is defined as the cumulative dose divided by treatment duration (mg/day).

Descriptive statistics of treatment duration, cumulative dose, dose exposure, average daily dose, and dose intensity, will be presented by treatment arm. In addition, descriptive statistics for treatment duration in weeks and associated frequency tables, as well as the number of cycles on study drug, will be presented by treatment arm.

The dosing statistics as described above may be presented by cycle for each treatment arm.

Dose reduction/interruption and re-escalation will be summarized. Summaries will include subjects who have at least one dose reduction/interruption due to AE, time to first dose reduction/interruption due to AE. Additional descriptive statistics will include, subjects who have a second dose reduction/interruption due to AE, duration of first and second dose reduction/interruption due to AE and interval between first and second dose reduction/interruption due to AE. The dose reduction/interruption and re-escalation may be presented by cycle for each arm.

10. PRIOR/CONCOMITANT MEDICATIONS

Prior medications (prescription and non-prescription) are defined as medications that were started before the start of the study treatment (whether or not ended before the start of the study treatment). Concomitant medications are defined as non-study medications that are started after the start of the first dose of the study drug and taken through the last dose of study drug.

All concomitant medication usage and procedures documented during the study period will be summarized in frequency tabulations for each treatment arm separately and pooled over all arms using the safety population. The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

Listings of prior/concomitant medications by subject will be provided.

11. EFFICACY ANALYSIS

Efficacy analysis will be performed on the intent-to-treat population. Adjudicated response as will be used for these analyses. Sensitivity analysis will be done based on investigator's assessment.

Subgroup analysis might be done by duration of treatment (completed 3 cycles vs. withdraw treatment by Cycle 4 Day 1).

Response

Response, including evaluation of minimal residual disease (MRD), will be assessed by iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008). The response rate based on the best response during the treatment period and the relative proportions in each response category will be examined. Distributions of the responses into the response categories (CR, CRi, nPR, PR, SD, PD) will be provided for each treatment arm. Response rates (CR+CRi+nPR+PR) together with confidence intervals will be provided for each regimen, both for the entire population and for the subgroups defined by the stratification factors.

Duration of Response

Duration of response is defined as the time from the first visit where PR, CRi, or CR was documented to PD. Duration of response will be censored at the last date that the subject was known to be progression-free for: 1) subjects who have not progressed at the time of analysis; 2) subjects who have withdrawn consent or are lost to follow-up prior to documentation of progression.

For subjects who achieved at least a PR, Kaplan-Meier product limit methods will be used to estimate the survival functions for each treatment arm. Median duration of response along with two-sided 95% confidence intervals (CIs) may be estimated.

Time to Response

Time to response is calculated as the time from randomization to the first documented date of PR, nPR, CRi or CR based on iwCLL guidelines.

Summary statistics (mean, median, SDev, min, max) of time to response will be presented by treatment arm.

Progression-free Survival (PFS)

Progression-free survival is calculated as the time from randomization to the first documented progression or death due to any cause during or after the treatment period, whichever occurs first. The progression date will be assigned to the earliest time when any progression is observed without prior missing assessments. If withdrawal of consent or loss to follow-up occurs before documented progression or death, then these observations will be censored at the date when the last complete tumor assessments determined a lack of progression.

For subjects who do not develop progressive disease at the time of analysis, if the response from the last visit was 'not evaluable', the most prior visit date with complete evaluation indicating no progressive disease will be used as the censor date.

For subjects who received other anti-CLL or anti-neoplastic therapy before PD, the most prior visit date with complete evaluation indicating no progressive disease will be used as the censor date.

If a subject has 2 or more consecutive missing response assessments followed by PD, the prior assessment date with complete evaluation indicating no progressive disease will be used as the censor date.

If a subject died without PD while in study but there are 2 or more consecutive missing response assessments before death date, the prior assessment date with complete evaluation indicating no progressive disease will be used as the censor date.

Kaplan-Meier product limit methods will be used to estimate the survival functions for treatment arm. Median PFS along with two-sided 95% CIs will be estimated.

Event-free Survival (EFS)

Event free survival (EFS) is the interval between the start of treatment to the first sign of disease progression, or treatment for relapse, or death (whichever occurs first).

The censoring rules are the same as PFS, execept that start of a new anti-CLL or anti-neoplastic therapy is considered an event.

Kaplan-Meier product limit methods will be used to estimate the survival functions for each treatment arm. Median EFS along with two-sided 95% CIs will be estimated.

Time-to-Progression (TTP)

TTP is defined as the time from randomization to the first documented progression. For subjects who do not progress during the study, TTP will be censored at the last adequate response assessment showing evidence of no disease progression. TTP is the same as PFS when there is no death. The same censoring rules for PFS applies except that death is not counted as an event.

Kaplan-Meier product limit methods will be used to estimate the survival functions for each treatment arm. Median TTP along with two-sided 95% confidence intervals (CI) will be estimated.

Overall Survival (OS)

Overall survival is calculated as the time from randomization to death from any cause. OS will be censored at the last date that the subject was known to be alive for subjects who were alive at the time of analysis and for subjects who have withdrawn consent or lost to follow-up before death was documented.

The analysis of OS will include survival information for all randomized subjects. Subjects who discontinued from the treatment phase of the study and who had possibly received other anti-cancer therapies and then subsequently died will be included in the analysis as death.

Kaplan-Meier product limit methods will be used to estimate the survival functions for each treatment arm and overall. Median OS along with two-sided 95% confidence intervals (CI) will be estimated.

12. SAFETY ANALYSIS

All safety analyses will be based on subjects who receive at least one dose of study drug and will be presented by treatment arm. Safety measurements will include adverse events, clinical laboratory information, vital signs, and deaths. All analyses of safety data will be conducted using the safety population unless specified otherwise.

12.1. Adverse Events

The adverse events of Neturopenia, Anemia and Thrombocytopenia will be analyzed according to the grading system as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008).

The adverse event of Tumor Lysis Syndrome (TLS) will be analyzed according to the grading system as recommended by Cairo-Bishop grading system.

Treatment emergent adverse events (AEs) will be summarized by treatment arm and overall. A treatment emergent adverse event is defined as any AE occurring or worsening on or after the first treatment of any study drug, and within 30 days after the last dose of the last study drug received. Adverse events will be presented in descending order of frequency (for all subjects) by SOC, and then within each SOC, by decreasing order of preferred term. Adverse events are documented on the CRF together with their severity, according to the NCI CTCAE version 3.0 or higher, also referred to as NCI toxicity grading. For the categorization of the adverse events, the MedDRA® dictionary (version 15.0) will be used.

AE frequency will be tabulated by body system, MedDRA preferred term for each treatment regimen during the Treatment Phase as well as for the Follow-up Phase when appropriate. In the by-subject analysis, a subject having the same event more than once will be counted only once and by the greatest severity. AEs will be summarized by worst NCI CTCAE version 3.0 grade. In the case that the AEs or event frequencies are judged to be clinically important, an exact test may be used to analyze the difference between the treatment arms. Events of interest will also be summarized by treatment cycles.

AEs leading to death or to discontinuation from treatment, events classified as NCI CTCAE version 3.0 Grade 3, 4, and 4 AEs, treatment-related events, serious adverse events (SAEs) and events of interest (including second primary malignancies) will be summarized separately.

Individual AE listings by subject will be provided.

As an exploratory analysis, AEs will be summarized by treatment arm and by subgroup (i.e., relapse vs. refactory, age <65 vs. age >=65, lines of prior CLL treatment, gender).

Adverse events (AE) will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 3.0 whenever possible.

12.2. Clinical Laboratory Evaluations

Laboratory data will be graded according to NCI CTCAE version 3.0. Shift tables demonstrating the changes from baseline to the worst severity grade observed during the treatment phase will be displayed for each treatment arm for relevant lab parameters for hematology, chemistry, and urinalysis.

12.3. Vital Sign Measurements

For vital signs, cross-tabulations showing the number of subjects with values below, within and above the normal ranges pre-treatment versus post-treatment will be summarized by treatment arm for the treatment phase. For weight, means, medians, standard deviations, minimum, and maximum will be provided by cycle. Percentage change of weight from cycle 1 day 1 will be summarized

12.4. Electrocardiogram (ECG)

ECG results by visit will be summarized by treatment arm. In addition, shift tables for ECG evaluations from baseline to the worst category during the treatment will be provided for each treatment arm.

12.5. Deaths

Deaths during the treatment phase and within 30 days from the last dose of study treatment will be tabulated by the primary cause of death and treatment arms. Separate summary tables will be made for the deaths that are suspected to drug related and for those that are considered non-drug related.

The same summary tables will be provided for the deaths that occur during follow-up phase separately.

13. OTHER TOPICS

13.1. Quality of Life

The Health-Related Quality of Life (HRQL) outcomes assessment include Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) and EQ-5D.

The subscale scores at each assessment as well as the changes from baseline for post-baseline assessments will be summarized and compared between treatment arms using repeated measures of ANOVA/ANCOVA using the baseline scores as covariates where appropriate. In addition, frequency tables for categorized change from baseline scores (Improvement, No Change, and Worsening) will be presented by treatment arm.

Various schemes will be assessed for missing data imputation if needed.

13.2. Pharmacokinetics Analysis:

If the data are sufficient, noncompartmental PK parameters, such as T_{max}, C_{max}, AUC, CL/F, and $t_{1/2}$, will be estimated. Descriptive statistics will be provided for plasma concentrations and PK parameters. Lenalidomide concentration data obtained from all visits may be used to develop the population PK model. The relationship between pharmacokinetics and response (biomarkers or clinical outcomes as appropriate) will be explored. Detailed methodology will be outlined in a separate PK data analysis plan and the results will be presented in a stand-alone PK report.

13.3. Regression Analyses

In addition we plan to perform both classical and Bayesian regression analyses in which predictors such as the stratification factors, treatment and possibly the treatment-by-stratification factor are included as covariates. Under the Bayesian framework these models will also be used to estimate posterior predictive probabilities for comparing the various treatments.

13.4. Subgroup Analysis

In addition to analyses that include all subjects, analyses will be performed to compare treatments within the following stratification subgroups:

- Relapsed vs. refractory to their last purine-analog or bendamustine based treatment regimen [relapsed/refractory as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)]. If a subject has received both, the status post most recent purine-analog or bendamustine treatment regimen will be used for stratification.
- Age < 65 years of age vs. ≥ 65 years of age

14. INTERIM ANALYSIS

14.1. Administration of the Interim Analyses

An independent DMC will be convened which will be composed of medical oncologists with experience in treating subjects with CLL and a statistician, all of whom are not otherwise involved in the study as investigators. An independent unblinded statistician will perform the interim analyses. The DMC will review safety data on an ongoing basis including adverse events and clinical laboratory data. During the course of the study, the DMC will review the efficacy data in accordance with the guidelines for the pre-planed interim analyses. Operational details for the DMC will be provided in the DMC charter.

The interim analysis results will not be disseminated among investigators and those directly involved with the study conduct unless recommended by the DMC.

14.2. Statistical Considerations

Adverse events will be summarized and assessed by the DMC first when at least 18 subjects have finished one treatment cycle. Then toxicity and progression will be assessed subsequently at 13-week intervals.

If a treatment arm is dropped then all new subjects will be randomized equally into the remaining arms.

The methods used to calculate the posterior probabilities are provided in protocol .

The interim analyses will be performed by a third party statistician not affiliated with Celgene.

15. REFERENCES

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