Title: An Open-Label, Dose-Escalation, Phase 1 Study of the Oral Formulation of MLN9708 Administered Weekly in Adult Patients With Relapsed or Refractory Light-Chain (AL) Amyloidosis Who Require Further Treatment

NCT Number: NCT01318902

SAP Approve Date: 06 November 2012

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

An Open-Label, Dose-Escalation, Phase 1 Study of the Oral Formulation of MLN9708 Administered Weekly in Adult Patients With Relapsed or Refractory Light-Chain (AL) Amyloidosis Who Require Further Treatment

Protocol #: C16007
Protocol Amendment #: 4

SAP Version:	Date of Statistical Analysis Plan:
Final Version 1.0	06 NOV 2012

PPD

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aninotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{tau}	area under the concentration-time curve, time 0 to end of dosing interval, estimated using the linear-log trapezoidal method
AUE	area under the effect versus time curve
BLQ	below limit of quantification
CL	clearance
C_{max}	maximum concentration
CSR	clinical study report
C_{trough}	predose concentration
CR	complete response
CRF	case report form
CV	coefficient of variation
CYP	cytochrome P_{450}
dFLC	serum differential free light chain concentration; difference between amyloid forming and non amyloid forming FLC
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOS	end of study
EOT	end of treatment visit
E_{max}	maximum observed inhibition value
FLC	free light chain
Ht	height
Hr	hour
INR	international normalized ratio
IV	intravenous; intravenously
λz	terminal disposition rate constant
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MLN2238	the complete hydrolysis product of MLN9708 to the boronic acid
MTD	maximum tolerated dose
NC	no change
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)

Abbreviation	Term
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QTc	rate-corrected QT interval (millisecond) of electrocardiograph
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
$t_{1/2}$	terminal disposition half-life
TE_{max}	time of occurrence of E_{max}
US	United States
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization
Wt	weight

TABLE OF CONTENTS

1. INTRODUCTION 6
1.1 Study Design 6
1.2 Study Objectives 7
1.2.1 Primary Objective 7
1.2.2 Secondary Objectives 7
1.2.3 Exploratory Objectives 7
2. POPULATIONS FOR ANALYSIS 8
2.1 Safety Population and Enrolled Patients 8
2.2 DLT-Evaluable Population 8
2.3 Organ Response-Evaluable Population 8
2.4 Hematological Response Evaluable Population 8
2.5 Pharmacokinetic Analysis Population 8
2.6 Pharmacodynamic Analysis Population 8
2.7 Protocol Deviation 8
3. HYPOTHESES AND DECISION RULES 9
4. INTERIM ANALYSIS 9
5. STATISTICAL METHODOLOGY 9
5.1 Sample Size Justification 9
5.2 Randomization and Stratification 10
5.3 Unblinding 10
5.4 Data Handling 11
5.4.1 Methods for Handling Missing Data 11
5.4.2 Definition of Baseline Values 11
5.4.3 Windowing of Visits 11
5.4.4 Justification of Pooling 11
5.5 Patient Disposition 12
5.6 Demographics and Baseline Disease Characteristics 12
5.6.1 Demographics 12
5.6.2 Medical History 12
5.7 Treatments and Medications 13
5.7.1 Concomitant Medications 13
5.7.2 Study Treatments 13
5.8 Efficacy Endpoints and Analyses 13
5.8.1 Efficacy Endpoints 14
5.8.2 Efficacy Analyses 16
5.9 Pharmacokinetic, Pharmacodynamic, and Exploratory Analysis 17
5.9.1 Pharmacokinetic Analyses 17
5.9.2 Pharmacodynamic Analyses 19
5.9.3 Exploratory Analysis 20
5.10 Safety Analyses 21
5.10.1 Adverse Events 21
5.10.2 Laboratory Data 23
5.10.3 Echocardiogram 25

5.10.4 Electrocardiogram....25
5.10.5 Vital Signs and Eastern Cooperative Oncology Group Performance Status....25
5.10.6 Pregnancy Test, Substance Use Data, and Other Data....26
6. CHANGES TO PLANNED ANALYSES FROM THE PROTOCOL....26
7. PROGRAMMING CONSIDERATIONS....26
7.1 Statistical Software....26
7.2 Rules and Definitions....26

1. INTRODUCTION

In general, the purpose of the statistical analysis plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This is an open-label, multicenter, phase 1, dose-escalation study of MLN9708 in adult patients with previously treated systemic light-chain (AL) amyloidosis. A 3 + 3 dose-escalation scheme will be implemented. Patients will receive escalating doses of MLN9708 orally (PO) on Days 1, 8, and 15 in a 28-day cycle in the absence of disease progression (PD) or unacceptable toxicity. If there is no hematologic response (complete response [CR], very good partial response [VGPR], or partial response [PR]) after completion of 3 cycles of single-agent MLN9708, dexamethasone will be added on Days 1 to 4 of every cycle (Days1-4 every 28 days) beginning with Cycle 4. The patient's response status will be reassessed after 3 additional cycles; if there is no hematologic response at that time, the patient will be removed from treatment and followed for survival.

Once the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) has been established, 2 expansion cohorts of patients with relapsed or refractory amyloidosis, including approximately 10 proteasome inhibitor-naïve patients and approximately 16 proteasome inhibitor-exposed patients, will be treated at the MTD/RP2D to more fully characterize the safety, tolerability, and efficacy of MLN9708, quality of life (QOL), and the pharmacokinetics (PK) and pharmacodynamics of MLN9708 in this patient population.

1.2 Study Objectives

1.2.1 Primary Objective

- To determine the safety, tolerability, and MTD of PO MLN9708 administered weekly in patients with previously treated relapsed or refractory AL amyloidosis
- To determine the RP2D of PO MLN9708 administered weekly

1.2.2 Secondary Objectives

- To characterize the plasma PK and whole blood pharmacodynamic effect of MLN9708 in this patient population
- To assess the rate of organ response and organ improvement according to standardized criteria
- To assess overall hematologic response rate (CR, VGPR, and PR)
- To assess time to hematologic and organ response
- To assess duration of hematologic and organ response
- To determine time to hematologic and organ disease progression
- To assess progression-free survival (PFS)
- To assess overall survival including 1-year survival rate

1.2.3 Exploratory Objectives

CCI

[redacted]

2. POPULATIONS FOR ANALYSIS

2.1 Safety Population and Enrolled Patients

The Safety population is defined as patients who receive at least 1 dose of MLN9708. The Safety population will be used for all safety analyses. In this study, the enrolled patients are the patients who received at least 1 dose of MLN9708.

2.2 DLT-Evaluable Population

The Dose-Limiting Toxicity (DLT)–Evaluable population is defined as patients who receive all Cycle-1 doses of MLN9708 or experience a DLT in Cycle 1 of the dose-escalation phase. The DLT-evaluable population will be used to determine the MTD.

2.3 Organ Response-Evaluable Population

The Organ Response-Evaluable population is defined as patients who receive at least 1 cycle of MLN9708, have amyloid involvement of at least kidney or heart at baseline, and have at least 1 postbaseline organ response assessment.

2.4 Hematological Response Evaluable Population

The Hematologic Response-Evaluable population is defined as patients who receive at least 1 cycle of MLN9708, have measurable disease at baseline, and have at least 1 post-baseline hematologic response assessment.

2.5 Pharmacokinetic Analysis Population

The PK Analysis population is defined as patients who receive at least 1 dose of MLN9708 and have sufficient MLN2238 concentration-time data and dosing data to permit the calculation of PK parameters.

2.6 Pharmacodynamic Analysis Population

The Pharmacodynamic Analysis population is defined as patients who receive at least 1 dose of MLN9708 and have sufficient whole blood 20S proteasome inhibition-time data to permit the calculation of pharmacodynamic parameters.

2.7 Protocol Deviation

A listing will be generated for major programmable protocol deviations. It will not affect analysis population definitions.

3. HYPOTHESES AND DECISION RULES

Not applicable for a phase 1 study

4. INTERIM ANALYSIS

As this is a phase 1 study, there is not a formal interim analysis. There will be an ongoing review of safety data with the medical monitor and study investigators.

5. STATISTICAL METHODOLOGY

Analyses will be primarily descriptive in nature. No formal statistical tests will be performed. Summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage (calculated using nonmissing values) per category for categorical data, unless specified otherwise.

Patients will be analyzed at the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

The analyses for the clinical study report (CSR) will be conducted after 75% of patients have PD or 12 months after last patient is enrolled, whichever occurs first in the study. At that time, all relevant data will be queried and cleaned; a database snapshot will be taken and used for the CSR. Additional follow-up treatment data will be entered into the database through study termination. Analyses may be updated based on additional information. An addendum to the CSR may be written if warranted based on these analyses. If deemed appropriate, however, the sponsor may decide to perform the analyses for CSR at the end of the study (EOS), which is approximately 2 years after the last patient is enrolled.

5.1 Sample Size Justification

A 3 + 3 dose-escalation scheme will be conducted, with 3 to 6 DLT-evaluable patients evaluated at each dose level. It is expected that as many as 30 patients will be enrolled in the dose-escalation part of this study.

Once the MTD/R2PD has been established, the following 2 expansion cohorts will be treated at the MTD or RP2D:

1. Proteasome inhibitor-naive expansion cohort including approximately 8 organ response-evaluable patients. There will be approximately 83% probability of observing at least 2 patients with organ responses among 8 patients based on the binomial probability calculation if the overall organ response rate is 35% for this population. Approximately 10 patients will be enrolled to obtain 8 response-evaluable patients.

2. Proteasome inhibitor-exposed expansion cohort including approximately 14 organ response-evaluable patients. There will be approximately 80% probability of observing at least 2 patients with organ responses among 14 patients based on the binomial probability calculation if the overall organ response rate is 20% for this population. Approximately 16 patients will be enrolled to obtain 14 organ response-evaluable patients.

Proteasome inhibitor-naïve patients are the patients who have not received any prior bortezomib contained therapy and the roteasome inhibitor-exposed patients are the patients who received at least one prior bortezomib contained therapy. Because approximately 6 patients in the dose-escalation part of the study will be included in the expansion cohorts, approximately 20 patients will be enrolled in the expansion part of this study. Please note that this is only for sample size justification, and the sponsor can stop the study enrollment for expansion cohorts at any time if deemed appropriate.

Overall, as many as 50 patients will be enrolled in this study.

5.2 Randomization and Stratification

No randomization or stratification will be performed in this study. Patients will be enrolled in successive dose cohorts during dose escalation. For the MTD disease expansion cohorts, patients will be enrolled in 1 of 2 expansion cohorts based on whether they have received a proteasome inhibitor-containing therapy.

5.3 Unblinding

As this is an open-label study; no unblinding methodology is required.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

Decisions regarding eligibility for this study may be made using local laboratory determinations in the dose-escalation segment of this study. For dosing decisions, local hematology and chemistry laboratory results may be used.

All available efficacy and safety data will be included in data listings. For summary tables, laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratories will be used only when no central laboratory test results exist at the same scheduled sample collection time point and when the local laboratory results support an adverse event (AE), dose modification, or other medical decision.

5.4.2 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but before, the start of study drug administration.

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

Refer to protocol Section 7.4.14 for details about the PK and pharmacodynamic sample collection windows.

5.4.4 Justification of Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

Due to the use of modified accelerated titration design for dose escalation, at a minimum, 1 patient will be dosed at any given dose level. Data may be pooled across dose levels for summary purposes. When appropriate, data will be summarized for patients at each dose level and pooled dose levels during dose escalation, patients at each expansion cohort (including the patients at MTD during dose escalation), all patients enrolled at the MTD dose level, and all patients overall.

5.5 Patient Disposition

A tabulation of patient disposition data will include a summary of the number of patients in the Safety, PK, and Pharmacodynamic analysis population, the DLT-Evaluable population, the Response-Evaluable population, and the primary reasons for study discontinuation. Patients will be considered to have completed the study if they:

- Have received at least 6 cycles of treatment, or
- Experience PD after completing at least 28 days of Cycle 1

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Demographic data (including age at date of informed consent, sex, race, ethnicity, height, and weight) will be summarized.

5.6.2 Medical History

5.6.2.1 General Medical History

Medical history findings will be presented in by-patient listings.

5.6.2.2 Disease Specific History

Baseline disease characteristics (such as amyloid involvement at study entry, cardiac biomarker stage at study entry, substance usage, Eastern Cooperative Oncology Group [ECOG] performance status, amyloidosis disease-related cardiac status, and amyloidosis disease-related neurologic status) will be summarized. Disease-specific history at initial diagnosis (time since initial diagnosis to first dose of MLN9708, amyloid involvement, cardiac biomarker stage, New York Heart Association classification) and the prior therapies (number of patients with prior therapy, lines of prior therapies, months from last dose of prior therapy to the first dose, best hematological response to prior therapy, and best organ response to prior therapy, type of prior therapy in the format of therapy contained, number of patients refractory to VELCADE, number of patients received VELCADE at last line of prior therapy, number of patients refractory to any line of prior therapy, number of patients refractory to last line of prior therapy) will be summarized.

All disease-specific characteristics, including agents received as prior therapy, will be presented in by-patient listings.

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from the first dosing date through the end of the on-study period will be tabulated by Anatomical Therapeutic Chemical (ATC) classification therapeutic subgroup and WHO drug preferred term.

Concomitant medication and procedures will be presented in by-patient listings.

5.7.2 Study Treatments

5.7.2.1 Extent of Exposure

A patient is considered to have been treated in a cycle as long as this patient receives any amount of study drug. A treatment cycle is defined as a cycle in which the patient received any amount of study drug.

Overall treatment duration will be summarized. The extent of exposure to MLN9708 will be summarize treatment duration, the number of cycles, total amount of dose taken in mg, total number of doses taken, dose intensity, relative dose intensity. The extent of exposure to dexamethasone will summarize the number of treatment cycles. The extent of exposure will be summarized by dose level, disease groups, and for all patients. Dose intensity (mg/cycle) will be calculated on a per-cycle basis, which equals the sum of total doses (mg) received in all cycles divided by the number of treatment cycles. Relative dose intensity is defined as 100*(Total amount of dose taken / Total prescribed dose over treated cycles), where total prescribed dose equals [dose prescribed at enrollment * number of prescribed doses per cycle * the number of treated cycles].

5.7.2.2 Dose Modifications

The modification actions on study drug will be summarized by dose level, disease groups, and for all patients, and by cycle if there are sufficient data for analysis.

5.8 Efficacy Endpoints and Analyses

Standard response criteria will be used in this study. The efficacy parameters include hematologic response rate, organ response rate, time to hematologic response, time to organ response, duration of hematologic response, duration of organ response, time to hematologic

disease progression, time to organ disease progression, hematologic disease PFS, organ disease PFS, and 1-year overall survival (OS) rate. The response assessment criteria are defined in the study protocol appendices.

5.8.1 Efficacy Endpoints

Best overall hematologic response is defined as the best hematologic response over time. It will be calculated and summarized in 2 time frames: (1) Up to the End of Treatment (EOT) visit; and (2) Up to the initiation of alternative antineoplastic therapy or EOS.

Hematologic objective response rate (ORR) is defined as the proportion of patients who achieved a PR or better response as best overall response in the Hematological Response-Evaluable population. Additional hematologic response rates are defined in the following table in the Hematological Response-Evaluable population. All the hematologic response rates will be calculated and summarized in 2 time frames: (1) Up to the EOT visit; and (2) Up to the initiation of alternative antineoplastic therapy or EOS.

Hematologic Response Rate:	**Proportion of Patients in the Hematological Response-Evaluable Population Whose Best Overall Responses Are:**
CR Rate	CR
VGPR Rate	VGPR
PR Rate	PR
No Change (NC) Rate	No Change (NC)
PD Rate	PD
ORR	PR or VGPR or CR
VGPR or better	VGPR or CR

Vital organ response is defined as the best response of either heart or kidney over time. Organ-specific response is defined as the best response of each defined organ over time. Organ response rate is defined as the proportion of patients who achieved certain response (including response, no change, and PD) in the Organ Response-Evaluable population. Organ-specific response rate will be calculated in the subgroup of the Organ Response-Evaluable population with amyloid involvement of the specific organ at baseline. All the above organ response rates will be calculated and summarized in 2 time frames: (1) Up to the EOT visit; and (2) Up to the initiation of alternative antineoplastic therapy or EOS.

Time to hematologic response is defined as the time from the date of the first dose of MLN9708 to the date of first documentation of a hematologic response (PR or better). Time to vital organ response is defined as the time from the date of the first dose of MLN9708 to

the date of first documentation of an organ response of either heart or kidney. In addition, time to best hematologic response is defined as the time from the date of the first dose of MLN9708 to the date of first documentation of the best hematologic response for each patient. The time-to-response endpoints apply only to the responders; therefore, there is no censoring. Hematologic responder is defined as a patient whose best hematologic response is PR or better. Vital organ responder is defined as a patient who demonstrates vital organ response. In addition, the responders will be determined in 2 time frames: (1) Up to the EOT visit; and (2) Up to the initiation of alternative antineoplastic therapy or EOS.

Duration of hematologic response is defined as the time from the date of first documentation of a hematologic response (PR or better) to the date of hematologic PD. Duration of vital organ response is defined as the time from the date of first documentation of an organ response of either heart or kidney to the date of organ PD. The duration-of-response endpoints apply only to the responders. However, the responders will be determined in two time frames: (1) Up to the EOT visit; and (2) Up to the initiation of alternative antineoplastic therapy or EOS. Patients will be censored in any of the following scenarios:

- If the patient starts an alternative antineoplastic therapy before the documentation of PD, then he or she will be censored at the date of the last available response assessment before the alternative antineoplastic therapy.

- If the patient has no documented PD and has not started alternative antineoplastic therapy and is still alive at the time of analysis, he or she will be censored at the date of the last available response assessment.

- If the patient died before the documentation of PD and had not started any alternative antineoplastic therapy, he or she will be censored at the date of the last available response assessment.

Time to hematologic disease progression is defined as the time from the date of the first dose of MLN9708 to the date of first documented hematologic PD. Time to organ disease progression is defined as the time from the date of the first dose of MLN9708 to the date of first documented organ PD. Patients will be censored in any of the following scenarios:

- If the patient starts an alternative antineoplastic therapy before the documentation of PD, then he or she will be censored at the date of the last available response assessment before the alternative antineoplastic therapy.

- If the patient has no documented PD and has not started alternative antineoplastic therapy and is still alive at the time of analysis, he or she will be censored at the date of the last available response assessment.

- If the patient died before the documentation of PD and had not started any alternative antineoplastic therapy, he or she will be censored at the date of the last available response assessment.

Hematologic disease PFS is defined as the time from the date of the first dose of MLN9708 to the date of documented hematologic PD or any death. Organ disease PFS is defined as the time from the date of the first dose of MLN9708 to the date of documented organ PD or any death. Patients will be censored in any of the following scenarios:

- If the patient starts an alternative antineoplastic therapy before the documentation of PD, then he or she will be censored at the date of the last available response assessment prior to the alternative antineoplastic therapy.

- If the patient has no documented PD and has not started alternative antineoplastic therapy and is still alive at the time of analysis, he or she will be censored at the date of the last available response assessment.

OS is defined as the time from the date of the first dose of MLN9708 to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. One-year OS rate is defined as the patient survival rate at 1 year after the date of the first dose of MLN9708.

5.8.2 Efficacy Analyses

The hematologic response (CR, VGPR, PR, no change [NC], PD) rate will be tabulated and analyzed based on the Hematologic Response-Evaluable population and presented with a 2-sided 95% exact binomial confidence interval. In addition, the overall hematologic response rates up to the end of Cycle 3 and up to the end of Cycle 6 will also be tabulated and analyzed in a similar way.

Vital organ response rate will be tabulated and analyzed based on the Organ Response-Evaluable population. Organ-specific response rate will be tabulated and analyzed based on in the subgroup of the Organ Response-Evaluable population with amyloid involvement of the specific organ at baseline. Estimates of the organ response rate will be presented with 2-sided 95% exact binomial confidence intervals.

Best hematologic response, time to hematologic response, time to best hematologic response, duration of hematologic response, time to hematologic PD, hematologic PFS, and OS will be presented in a by-patient listing. Vital organ response, organ-specific response, time to vital organ response, duration of vital organ response, time to organ PD, organ PFS, and OS will be presented in a by-patient listing.

Time to hematologic response, time to best hematologic response, duration of hematologic response, time to hematologic PD, hematologic PFS, and OS (1-year OS rate) will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates, if appropriate.

Raw values of serum M-protein, urine M-protein, serum free light chain (FLC), and the difference between amyloid-forming and nonamyloid-forming free light chain (dFLC), as well as the change from baseline, will be presented in by-patient listings. A waterfall plot will be generated to display the maximum change from baseline in dFLC.

QOL will be assessed for patients in the expansion cohorts only using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30, multiple myeloma module). Descriptive statistics will be presented for both the actual values and the changes from baseline in EORTC-QLQ-C30 assessment over time. EORTC-QLQ-C30 assessments will be analyzed to determine if hematologic response to therapy is accompanied by measurable improvement in QOL.

5.9 Pharmacokinetic, Pharmacodynamic, and Exploratory Analysis

5.9.1 Pharmacokinetic Analyses

The PK Analysis population will be used for the description of the PK profile and for the estimation of PK parameters.

PK evaluation will be based on concentrations of MLN2238, the complete hydrolysis product of MLN9708, in specimens collected at prespecified times before and after drug administration. Actual sample collection times will be used for the calculation of PK parameters. In the event that actual collection times are either unreliable or missing, scheduled collection times will be used. For ease of presentation, scheduled collection times will be used to present results in tables and figures. Both scheduled and actual collection times will be presented in listings.

Concentrations of MLN2238 that are below the limit of quantification (BLQ) will be treated as zero. Concentration data that are considered anomalous may be excluded from the concentration summaries and plots and will not be used in the calculation of PK parameters. Evidence or explanation will be provided to justify the exclusion of data.

When summarizing concentrations or PK parameters, a minimum of 2 values is required to show the mean and geometric mean, and at least 3 values are required to show the standard deviation and coefficient of variation (CV). Summary statistics will be reported only if the calculated mean value is greater than the lower limit of quantification (LLOQ) and at least 50% of the values are nonzero.

5.9.1.1 Plasma and Whole Blood Pharmacokinetic Profiles

Individual patient plasma and whole blood concentration data will be listed. Concentrations will be summarized (N, mean, standard deviation, CV, geometric mean, median, min, and max) according to dose cohort and dosing cycle and day. Population mean and individual plasma and whole blood concentration-time data will be plotted by dose cohort and dosing cycle and day.

5.9.1.2 Plasma and Whole Blood Pharmacokinetic Parameters

The following PK parameters will be calculated by noncompartmental methods, as data permit, from concentration-time data:

Parameter	Definition	Units
C_{max}	Observed maximum concentration	ng/mL
T_{max}	First time Cmax is observed	hr
C_{trough}	Observed concentration at the end of a dosing interval	ng/mL
AUC_{tau}	Area under the concentration-time curve, time 0 to end of dosing interval, estimated using the linear-log trapezoidal method	hr*ng/mL
$lambda_z$	Terminal disposition phase rate constant	1/hr
$t_{1/2}$	Terminal disposition phase half-life	hr
Rac	Accumulation ratio	unitless

Different PK parameters are to be estimated following dosing on Day 1 and Day 15. For some of the doses, concentration data is collected only on either Day 1 or on Day 15. PK parameters will be calculated accordingly. The PK parameters to be estimated for each day of dosing are as follows:

	Dosing Day	
PK Parameter	**1**	**15**
C_{max}	X	X
T_{max}	X	X
C_{trough}	X	X
AUC_{tau}	X tau = 168 hr	X tau = 168 hr
$lambda_z$		X
$t_{1/2}$		X
Rac		X

Individual patient parameter data will be listed. PK parameters will be summarized (N, mean, standard deviation, CV, geometric mean [as appropriate], median, min, and max) according to dose cohort and dosing cycle and day.

5.9.2 Pharmacodynamic Analyses

The Pharmacodynamic Analysis population will be used for the description of the pharmacodynamic profile and for the estimation of pharmacodynamic parameters.

The pharmacodynamic measure that will be analyzed is whole blood 20S proteasome inhibition. The inhibition is defined as the postdose proteasome activity times divided by the baseline proteasome activity. If the baseline proteasome activity is missing or is BLQ for a patient, then no inhibition will be calculated for that patient. Individual and mean whole blood 20S proteasome inhibition data will be plotted over time, and summary tabulations will be presented.

Actual specimen collection times will be used for the calculation of pharmacodynamic parameters. In the event that actual collection times are either unreliable or missing, scheduled collection times will be used. For ease of presentation, scheduled collection times will be used to present results in tables and figures. Both scheduled and actual collection times will be presented in listings.

Proteasome activity measurements that are BLQ will be treated as zero. Proteasome activity measurements that are considered anomalous may be excluded from data summaries and plots and will not be used in the calculation of pharmacodynamic parameters. Evidence or explanations will be provided to justify the exclusion of data.

When summarizing proteasome inhibition or pharmacodynamic parameters, a minimum of 2 values is required to show the mean, and at least 3 values are required to show the standard deviation and CV. Summary statistics will be reported only if at least 50% of the values are nonzero.

5.9.2.1 Pharmacodynamic Profiles

Individual patient proteasome activity data and proteasome inhibition data will be listed. Proteasome inhibition will be summarized (N, mean, standard deviation, CV, median, min, and max) according to dose cohort and dosing cycle and day. Population mean and individual proteasome inhibition-time data will be plotted by dose cohort and dosing cycle and day.

5.9.2.2 Pharmacodynamic Parameters

The following pharmacodynamic parameters will be calculated by noncompartmental methods, as data permit, from proteasome inhibition-time:

Parameter	Definition	Units
E_{max}	Observed maximum proteasome inhibition	%
TE_{max}	First time Emax is observed	hr
AUE_{tau}	Area under the inhibition-time curve from time 0 to end of dosing interval (0-168 hours) estimated using the linear trapezoidal rule	hr*%

Individual patient parameter data will be listed. Pharmacodynamic parameters will be summarized (N, mean, standard deviation, CV, median, min, and max) according to dose cohort and dosing cycle and day.

In addition to the noncompartmental PK and pharmacodynamic analyses described in Section 5.9.1 and Section 5.9.2, PK and pharmacodynamic data collected in this study may be used for population PK and PK/pharmacodynamic modeling purposes. These analyses will be reported separately, as they will use PK and/or pharmacodynamic data collected in other clinical studies.

5.9.3 Exploratory Analysis

5.9.3.1 Tumor Biomarker Analysis

CCI [redacted]

CCI

[redacted]

5.9.3.2 Germline DNA Polymorphism Analysis

CCI

[redacted]

5.10 Safety Analyses

These analyses will be performed using the Safety population.

5.10.1 Adverse Events

5.10.1.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study drug or until start of subsequent antineoplastic therapy; any event that is considered drug-related regardless of the start date of the event; or any event that is present at baseline but worsens in severity after baseline. Patients who experience the same AE more than once will have that event counted only once within each body system, once within each High Level Term, and once within each Preferred Term.

AEs will be tabulated by System Organ Class, High Level Term, and Preferred Term. Summary tabulations include the following subsets:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs

- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Grade 3 treatment-emergent AEs and Grade 4 treament-emergent AEs
- Grade 3 drug-related treatment-emergent AEs and Grade 4 drug-related treament-emergent AEs

Treatment-emergent AEs will be tabulated by System Organ Class, Preferred Term, and highest intensity. The most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by Preferred Term. In addition, a by-patient listing of the treatment-emergent AEs will be presented.

AEs with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has a month and year but the day is missing, the event will be considered treatment emergent if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of MLN9708 and on or before the month and year of the date of the last dose of MLN9708 plus 30 days.
- If the start date has a year, but the day and month are missing, the event will be considered treatment emergent if the year of the start date of the event is on or after the year of the date of the first dose of MLN9708 and on or before the year of the date of the last dose of MLN9708 plus 30 days.
- If the start date of an event is completely missing, then the event is assumed to be treatment emergent.

5.10.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent serious AE (SAE) will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term. A similar table for drug-related SAEs will also be presented.

A by-patient listing of the SAEs will be presented (the listing will contain all SAEs regardless of treatment-emergent AE status).

5.10.1.3 Deaths

A listing of on-study deaths will be presented. On-study death is defined as death events that occur within 30 days of the last dose of study drug.

5.10.1.4 Adverse Events Resulting in Discontinuation of Study Drug or Study Drug Modification

A by-patient listing of AEs resulting in discontinuation of study drug will be presented. The number and percentage of patients experiencing at least 1 AE resulting in discontinuation of study drug will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term.

A by-patient listing of AEs resulting in study drug modification will be presented. The number and percentage of patients experiencing at least 1 AE resulting in study drug modification will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term.

All AEs resulting in discontinuation of study drug occurring on-study will be displayed.

5.10.1.5 Dose Limiting Toxicities

A by-patient listing of DLTs that occur during Cycle 1 of treatment will be presented by dose level for all patients enrolled during the dose-escalation portion of this study. Patients will be grouped by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

5.10.2 Laboratory Data

For hematology parameters and chemistry parameters, shift tables of the change in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) from baseline to the worst postbaseline CTCAE grade will be generated. If necessary, graphical displays will be used to show changes in laboratory measures over time for each individual patient by the line graphs of individual tests over time for each patient

In addition, the lines of mean estimates over time by linear mixed model may be graphed for a selected list of test parameters.

Panel	Test	CTCAE Shift Table	Line Graphs
Chemistry	Albumin	X	X
	ALT	X	X
	AST	X	X
	Alkaline Phosphatase	X	X
	Creatinine	X	X
	Bilirubin	X	X
	Phosphate	X	X
	Uric Acid	X	
	Calcium	X	X
	Magnesium	X	X
	Potassium	X	
	Sodium	X	
	Glucose	X	
Hematology	Platelet	X	X
	Hematocrit		
	Hemoglobin	X	X
	White Blood Cells (WBC)	X	
	Lymphocytes	X	X
	Neutrophils (ANC)	X	X
Cardiac markers	NT-ProBNP		X
	BNP		X
	Troponin T		X
24 hours urine collection	Total protein		X
	Creatinine Clearance		X

In addition, the coagulation parameters and urinalysis parameters will be presented in by-patient listings and are listed below:

- Coagulation (from patients in the tumor pharmacodynamic expansion cohort and in the MTD disease expansion cohort to undergo tumor biopsy): prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Urinalysis: appearance and color, blood, pH, nitrite, specific gravity, urobilinogen, protein, glucose, ketones, leukocyte esterase, and bilirubin
- Hormones: thyrotropin (TSH) and cortisol
- β2-microglobulin

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a nonnumeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

5.10.3 Echocardiogram

The values of mean left ventricular wall thickness (septum and posterior wall) and the left ventricular ejection fraction (LVEF), as well as their changes from baseline, will be presented in a listing.

5.10.4 Electrocardiogram

Electrocardiogram (ECG) clinical results (within normal limits; abnormal, not clinically significant; abnormal, clinically significant) will be presented in a by-patient listing and in a summary table.

ECG intervals (PR interval and heart rate, and calculated corrected QT [QTc] intervals) will be summarized at each scheduled time point, along with mean change from baseline to each posttreatment time point.

QTc (Bazett [QTcB] and Fridericia [QTcF] corrections) will be calculated as follows:

R-R interval = 60 /heart rate

$QTcF = QT\ Interval/(R\text{-}R\ Interval)^{1/3}$

$QTcB = QT\ Interval/(R\text{-}R\ Interval)^{1/2}$

5.10.5 Vital Signs and Eastern Cooperative Oncology Group Performance Status

Listings will be generated for displaying the vital sign parameters and ECOG performance status over time. The descriptive statistics for the actual values and changes from baseline in vital sign parameters over time will be summarized by scheduled time point. A table of ECOG performance status shifts from baseline to worst post baseline assessment will be generated.

5.10.6 Pregnancy Test, Substance Use Data, and Other Data

The pregnancy test, substance use and any other collected important data will be presented in by-patient listings.

6. CHANGES TO PLANNED ANALYSES FROM THE PROTOCOL

The definition of the PK-Evaluable popuplation and the Pharmacodynamics-Evaluable popuplation are to be changed to include all treated patients instead of patients receiving full doses during Cycle 1 and to remove the condition of "did not receive any excluded concomitant medications".

The 2 major organs (heart and kidney) will be called vital organs in the SAP and analyses.

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.2 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Patient populations are defined in Section 2.

Treatment-emergent AEs are defined in Section 5.10.1.1.