



Title: An Open-Label, Phase 1, Dose Escalation Study of MLN2480 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients With Metastatic Melanoma

NCT Number: NCT01425008

SAP Approve Date: 29 July 2016

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, Phase 1, Dose Escalation Study of MLN2480 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients With Metastatic Melanoma

Protocol #: C28001

SAP Version:
Final

Date of Statistical Analysis Plan:
29July2016

Approval Signatures

PPD



TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	4
1. INTRODUCTION.....	6
1.1 Study Design.....	6
1.2 Study Objectives	7
1.2.1 Primary Objectives	7
1.2.2 Secondary Objectives.....	7
1.2.3 Exploratory Objectives	7
2. POPULATIONS FOR ANALYSIS	8
2.1 DLT-evaluable population.....	8
2.2 Response-Evaluable Population.....	8
2.3 Safety Population	8
2.4 Pharmacokinetics evaluable Population	8
2.5 Pharmacodynamics evaluable Population	8
3. HYPOTHESES	8
4. INTERIM ANALYSIS.....	9
4.1 Interim Analysis	9
4.2 Data Safety Monitoring Board (DSMB).....	9
5. STATISTICAL METHODOLOGY	9
5.1 Sample Size Justification.....	9
5.2 Randomization and Stratification.....	9
5.3 Unblinding	10
5.4 Data Handling	10
5.4.1 Methods for Handling Missing Data.....	10
5.4.2 Definition of Baseline Values	11
5.4.3 Windowing of Visits.....	12
5.4.4 Justification of Pooling	12
5.4.5 Withdrawals, Dropouts, Loss to Follow-up	12
5.5 Patient Disposition	12
5.6 Demographics and Baseline Disease Characteristics.....	12
5.6.1 Demographics.....	12
5.6.2 Medical History	13
5.6.3 Baseline Disease Status.....	13
5.7 Treatments and Medications	13
5.7.1 Concomitant Medications	13
5.7.2 Study Treatments	13
5.8 Efficacy Analyses.....	14
5.9 Pharmacokinetic, Pharmacodynamic, and Pharmacogenetics Analysis.....	14
5.9.1 Pharmacokinetic Analyses	14
5.9.2 Pharmacodynamic Analyses.....	19
5.9.3 Pharmacogenetics Analyses	20
5.10 Safety Analyses	20
5.10.1 Adverse Events	20
5.10.2 Laboratory Data	22

MLN-2480
Statistical Analysis Plan, Study C28001

5.10.3 Electrocardiograms 22
5.10.4 Vital Signs 23
5.10.5 Other Safety Assessments 23
6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL 23
7. PROGRAMMING CONSIDERATIONS 23
7.1 Statistical Software 23
7.2 Rules and Definitions 23
8. REFERENCES 24

on-commercial use only and subject to the applicable Terms of Use

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BLQ	below level of quantification
CI	confidence interval
CL _R	renal clearance
C _{max}	maximum plasma concentration
CR	complete response
C _{trough}	trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P ₄₅₀
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ERK	extracellular signal-regulated kinase
CCI	
IL	interleukin
K _i	Inhibition constant
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NALQ	number of observations above lower limit of quantitation
NCI	National Cancer Institute
ORR	overall response rate
PD	progressive disease (disease progression)
pERK	phosphorylated extracellular signal-regulated kinase
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
Q2D	every other day
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease

MLN-2480
Statistical Analysis Plan, Study C28001

Abbreviation	Term
$t_{1/2z}$	Terminal disposition phase half-life
T_{max}	first time to maximum plasma concentration
TEAE	Treatment Emergent Adverse Event
TTR	time to response

on-commercial use only and subject to the applicable Terms of Use

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 a phase 1, multicenter, nonrandomized, open-label, dose escalation study. The study is conducted in 2 phases (dose escalation and dose expansion) and will test 2 dosing schedules (every other day (Q2D) and once weekly (QW)) of MLN2480 also known as TAK-580.

In the Dose Escalation phase, a 3 + 3 dose escalation design is implemented to evaluate MLN2480 Q2D or QW in dose intervals with continuous dosing (no washout) prespecified in the [Dose Escalation Algorithm](#). Patients in the Dose Escalation cohorts are evaluated for dose-limiting toxicity (DLT) during the first cycle of treatment, and decisions regarding escalation to the next dose level, expansion of a dose level, or evaluation of an intermediate dose level are determined based on DLT evaluation. Patients in the Dose Escalation phase may continue treatment for additional cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

The dose used for the Dose Expansion phase (MTD and/or RP2D) is selected based on data from the Dose Escalation phase at the corresponding dosing schedule (Q2D or QW). The Dose Expansion phase may commence before establishing the MTD/RP2D upon medical determination of a safe dose that is lower than MTD/RP2D. Patients fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of MLN2480. Patients in the Dose Expansion phase take MLN2480 orally Q2D or QW in 28-day cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

Patients who discontinue study treatment during Cycle 1 for reasons other than MLN2480-related toxicity are replaced in the Dose Escalation phase of the study.

A total of approximately 198 patients with solid tumors will be enrolled in this study (approximately 54 patients in the Dose Escalation phase [Q2D and QW] and approximately 144 patients in the Dose Expansion phase [Q2D and QW]). Of the approximately 144 patients enrolled in the Dose Expansion phase, approximately 128 patients with locally advanced metastatic and/or unresectable melanoma (each cohort with a maximum of 16 patients) and 16 patients with advanced solid tumors (excluding lymphoma) will be enrolled.

MLN-2480
Statistical Analysis Plan, Study C28001

When patients discontinue study treatment, they return to the study site 30 (+ 10) days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, to complete the End of Study visit procedures. All MLN2480-related toxicities are followed until the End of Study visit or until the toxicities have resolved, stabilized, or returned to baseline, whichever occurs later.

1.2 Study Objectives

1.2.1 Primary Objectives

The primary objectives of the study are as follows:

- To evaluate the safety and tolerability of MLN2480 taken orally Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation phase and Dose Expansion phase and Pharmacokinetic (PK) Expansion cohort) or locally advanced, metastatic, and/or unresectable melanoma (Dose Expansion phase).
- To determine the MTD of MLN2480 taken Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation phase).
- To determine the recommended phase 2 dose (RP2D) of MLN2480 taken Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation phase).

1.2.2 Secondary Objectives

The secondary objectives in this study population are as follows:

- To evaluate the preliminary efficacy of MLN2480 as measured by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
- To evaluate the pharmacokinetics of MLN2480.
- To evaluate the effect of MLN2480 on pharmacodynamic markers in paired tumor biopsies.

1.2.3 Exploratory Objectives

CCI



2. POPULATIONS FOR ANALYSIS

2.1 DLT-Evaluable Population

The DLT-evaluable population is defined as all patients in the Dose Escalation phase of the study who either experience DLT during Cycle 1 or complete at least 75% of the planned doses of MLN2480 and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. This population will be used for analysis of MTD.

2.2 Response-Evaluable Population

The response-evaluable population is defined as all patients with measurable disease who receive any amount of MLN2480 and have at least 1 post baseline response assessment. This population will be used for response related analyses (eg, ORR, DOR, etc).

2.3 Safety Population

The safety population is defined as all patients who receive at least 1 dose of study drug (MLN2480). This population will be used for all safety analyses, as well as other analyses such as pharmacogenomic analyses except the response related analyses.

2.4 Pharmacokinetics Evaluable Population

The PK-evaluable population is defined as all patients who have sufficient dosing data and MLN2480 concentration-time data to permit calculation of any MLN2480 PK parameters.

Assessment of PK evaluability will be performed for patients undergoing serial PK sampling in dose escalation and PK expansion cohorts and will not include patients undergoing sparse PK sampling in melanoma expansion cohorts. The PK evaluable population will be used for the description of the serial PK profile of MLN2480 and for the estimation of PK parameters via noncompartmental analysis.

2.5 Pharmacodynamics Evaluable Population

The pharmacodynamic evaluable population is defined as all patients who have sufficient dosing data and pharmacodynamic data, collected within the protocol-specified window of sampling time. The pharmacodynamic evaluable population will be used for calculation of summary statistics and graphical analysis.

3. HYPOTHESES

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed.

4. INTERIM ANALYSIS

4.1 Interim Analysis

No formal interim analysis will be performed. Safety and available PK data will be reviewed jointly by sponsor and investigators on an ongoing basis for the purposes of safety monitoring and dose escalation decisions.

4.2 Data Safety Monitoring Board (DSMB)

There is no DSMB in this study.

5. STATISTICAL METHODOLOGY

In general, 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 percent (of non-missing) per category for categorical data, unless specified otherwise.

At the time of CSR database lock, all relevant data will be queried and cleaned; a database snapshot will be taken and used for the CSR. Additional 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 at study termination.

Unless specified otherwise, all the summary tables will be presented by each dose level cohort at escalation, subtotal of Q2D patients at escalation, subtotal of QW patients at escalation, total at escalation, each expansion cohort, total at expansion, and if applicable, subtotal of Q2D patients at expansion, subtotal of QW patients at expansion.

5.1 Sample Size Justification

The total sample size for the study will be approximately 198 patients (approximately 54 patients in the Dose Escalation phases (Q2D and QW) and approximately 144 patients in the Dose Expansion phase [Q2D and QW]). In the Dose Escalation phase, a 3 + 3 dose escalation design will be used; therefore, the sample size is dependent on the number of dose escalation steps and the number of patients per cohort. To further evaluate the safety and preliminary antitumor activity of the selected MLN2480 dose for the Dose Expansion phase, approximately 128 patients with locally advanced, metastatic, and/or unresectable melanoma (each cohort will have a maximum of 16 evaluable patients) and 16 patients with advanced solid tumors (excluding lymphoma) will be enrolled in the Dose Expansion phase (Q2D and QW).

5.2 Randomization and Stratification

Randomization is not used in this study; however, patients are assigned to 1 of 8 Expansion cohorts based on tumor type, mutational status, and/or treatment history (see Section 5.1 of the protocol). No stratification is planned for this study. An interactive voice response system is used for cohort management. Refer to the Study Manual for details.

5.3 Unblinding

This is an open-label study. No unblinding methodology is required.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available data will be presented. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures. No data imputation will be applied for missing values unless specified.

5.4.1.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

1. If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the 15th will be used.
2. If only the year is present, and it is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the first of January will be used.
3. If only the year is present, and it is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicates that the date is earlier.

5.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies

5.4.1.2.1 Missing/Partial Dates in Adverse Events

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

1. If the stop date has month and year but day is missing, the last day of the month will be imputed.
2. If the stop date has year, but day and month are missing, the 31st of December will be imputed.

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

If the stop date of an adverse event is completely missing, then this event will be regarded as ongoing and will be included in the summary table.

Adverse events with start dates that are completely or partially missing will be imputed as follows:

1. If the start date has month and year but day is missing.
 - a. If the onset month and year are the same as that of first dose date, the first dose date will be used instead. If the onset month and year are different from that of the first dose date, then the first day of the month will be used.

- b. After imputation, the imputed dates will be compared against the stop date. If this date is later than the stop date (possibly imputed), then the stop date will be used instead.
2. If the start date has year, but day and month are missing.
 - a. If the onset year is the same as that of first dose date, then the first dose date will be used instead
 - b. If onset year is different than that of the first dose date, the first of January of the year will be imputed.
 - c. After the imputation, the imputed dates will be compared against the dose stop date. If this date is later than the stop date (possibly imputed), then the stop date will be used instead.
 3. If the start date of an adverse event is completely missing, then it is imputed with the first dose date.

5.4.1.2.2 Missing/Partial Dates in Concomitant Therapies

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

1. If the start date has month and year but day is missing, the therapy will be included in the summary table if the month and year are:
 - a. On or after the month and year of the date of the first dose of study drug and
 - b. On or before the month and year of the date of the last dose of study drug plus 30 days.
2. If the start date has year, but day and month are missing, the therapy will be included in the summary table if the year is:
 - a. On or after the year of the date of the first dose of study drug and
 - b. On or before the year of the date of the last dose of study drug plus 30 days.

If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is prior to the date of the first dose of study drug, then this therapy will not be included in the summary table.

If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is on or after the date of the first dose of study drug, then the therapy will be included in the summary table.

If the start date and stop date of concomitant therapies are completely missing, then the therapy will be included in the summary table.

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 prior to, the start of study drug administration. For the triplicate electrocardiogram (ECG) summaries in the Dose Escalation and PK Expansion cohorts, the

baseline is defined as the average of the triplicate 12-lead ECG measurements recorded at 2 to 5 minute intervals on Cycle 1, Day 1 before dosing (predose).

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

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. If differences between sites are noted through the review process, exploratory analysis may be performed to assess the differences.

5.4.5 Withdrawals, Dropouts, Lost to Follow-up

Patients will be replaced if they are not evaluable for DLT during cycle 1 in the Dose Escalation Phase. These additional patients will receive the same allocation of treatment as those whom they replaced.

Time to event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events (progressive disease /death).

5.4.6 General Conventions for Determining Duration

The duration of an event is calculated as: date of end of the event – date of start of the event +1, eg, days on treatment = date of last dose – date of first dose + 1.

Time to event analyses such as survival time or time to tumor progression are calculated in a similar way. Table shells will specify if there are any exceptions

5.5 Patient Disposition

Disposition of patients includes the number and percentage of patients for the following categories: safety population, PK-evaluable population, pharmacodynamic-evaluable population, response-evaluable population, DLT-evaluable population. These categories will be summarized in each dose group and total for Dose Escalation phase, for the PK expansion and other expansion cohorts and the total for Expansion Phase. The primary reason for study discontinuation will also be summarized in this table. All percentages will be based on the number of patients in the safety population.

5.5.1 Protocol Deviations

A listing of major protocol deviations will be provided.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Demographics will be summarized for the safety population. Demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, body surface area and other

MLN-2480
Statistical Analysis Plan, Study C28001

parameters as appropriate. No inferential statistics will be carried out. Demographic data will also be presented in a by-patient listing.

Age is calculated from date of birth to date of informed consent.

Body surface area (m²) = {[height(cm) x weight(kg)]/3600}^{1/2}

5.6.2 Medical History

Medical history data will be presented in a by-patient listing, including medical and surgical history, date of onset and status (ongoing or resolved).

5.6.3 Baseline Disease Status

Baseline disease characteristics consist of baseline Eastern Cooperative Oncology Group (ECOG) score, primary diagnosis, years since initial diagnosis, method of stage classification, disease stage at study entry and disease-specific markers.

By-patient listings will also be presented for baseline disease characteristics.

A separate table will summarize the numbers and percentages of patients who had prior therapies, including prior antineoplastics, prior radiation therapy, prior surgery and best response to the last therapy. Separate by-patient listings will also be presented.

5.7 Treatments and Medications

5.7.1 Concomitant Medications and Procedures

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from the first dose date through 30 days after last dose data will be tabulated by the Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term. Concomitant medications will also be presented in a by-patient listing.

Concomitant procedures will not be coded, but will be presented in a by-patient listing.

5.7.2 Study Treatments

MLN2480 is administered Q2D or QW. MLN2480 is formulated as an immediate release tablet for oral administration.

5.7.2.1 Extent of Exposure

The exposure to study drug will be summarized by total amount of dose received (mg), total number of doses received, number of treated cycles, numbers and percentages of patients who had ≥ 1 , ≥ 2 , ..., and ≥ 13 treated cycles, and relative dose intensity.

A treated cycle is defined as a cycle in which the patient received any amount of study drug.

Planned dose is determined by the dose level to which a patient is enrolled at study entry.

Relative Dose intensity (%) is defined as $100 \times (\text{total dose received (mg)}) / (\text{planned total dose per day} \times \text{planned total number of treated days per cycle} \times \text{number of treated cycles})$.

MLN-2480
Statistical Analysis Plan, Study C28001

Dosing data will also be presented in by-patient listings.

The actions on study drug (Reduced, Increased, Held, Missed, Interrupted, Cycle Delay, Delayed within a Cycle, or Discontinued Permanently) will be summarized by treatment cycles (each of Cycle 1 through Cycle 6, Cycle 7-12, Cycle ≥ 13 , and total).

5.8 Efficacy Analyses

As this is a phase I study, analysis of efficacy measures will be descriptive. Antitumor activity of MLN-2480 will be based on the best overall response. Disease response will be determined by investigators at each time point. The best overall response is defined as the best response recorded from the start of the study treatment until the End of Study visit using the RECIST guideline (version 1.1). The number and percentage of patients will be summarized by the best overall disease response category (ie, complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]). Disease response category will also be presented in a by-patient listing.

Overall response rate (ORR) is defined as the proportion of patients whose best overall response is either CR or PR. ORR will be tabulated with point estimates. Confidence intervals (95% CIs) will be provided for each expansion cohort as well as the total for the expansion cohorts and total for the escalation cohorts.

Time to response (TTR) is defined as the time from the date of first dose of study treatment to the date of the first documentation of a PR or better response up to the alternative therapy in a patient who responded. TTR will be summarized and listed.

Duration of response (DOR) will be assessed from the date of first documented response (CR or PR) to the date of first documented PD and will be censored at the date of the last assessment for responders who die without documented PD and for responders who are still alive and have not progressed. DOR will be summarized and listed.

Progression-free survival (PFS) is defined as the time from the date of first study drug administration to the date of first documented PD or death due to any cause, whichever occurs first. PFS will be censored at the last response assessment that is SD or better for a patient that has not progressed and last known to be alive. Patients with no response assessment will be censored at the date of first dose. PFS will be summarized and listed.

Time-to-event data for each melanoma expansion cohort and the total of the expansion cohorts and total of the escalation cohorts will be analyzed by the Kaplan-Meier method and results will be summarized by 25th, 50th (median) and 75th percentiles with associated 2-sided 95% CIs, as well as the percentage of censored observations.

5.9 PK, Pharmacodynamic, and Pharmacogenetics Analysis

5.9.1 PK Analyses

PK Assessments

Blood and urine samples will be collected for measurement of plasma and urine MLN2480 concentrations in patients in the escalation and expansion cohorts at time points designated in the protocol. Validated bioanalytical methods will be used for the determination of MLN2480 concentrations in plasma and urine.

Methods for PK Data Handling

No data imputation will be applied for missing concentration values, with one exception. If the end of dosing interval (trough) plasma concentration value is missing after Cycle 1, Day 21 dosing, that concentration may be imputed at the discretion of the Clinical Pharmacologist for the purpose of calculating Cycle 1, Day 21 PK parameters (eg, C_{trough} , PTR, AUC_{tau}) that depend on the end of dosing interval plasma concentration. Additionally, if the time between Cycle 1, Day 21 dosing time and actual sample collection time for the Cycle 1, Day 21 end of dosing interval (trough) plasma sample is less than 40 hr (approximately 20% deviation from the scheduled sample collection time of 48 hr in the case of Q2D dosing), that concentration may be imputed at the discretion of the Clinical Pharmacologist for the purpose of calculating Cycle 1, Day 21 PK parameters that depend on the end of dosing interval plasma concentration. If imputation is performed, the end of dosing interval plasma concentration will be set equal to the pre-dose plasma concentration for the same dosing interval. Imputation will be performed only if it can be inferred that PK steady-state conditions are attained by Cycle 1, Day 21.

Pharmacokinetic Profiles for MLN2480

The PK evaluable population will be used for the description of the serial PK profile of MLN2480.

For Dose Escalation and PK Expansion cohorts, plasma concentrations of MLN2480 will be summarized by time post-dose and grouped by dose group and dosing cycle and day. If the same dose is administered in a Dose Escalation and the PK Expansion cohort, the plasma concentration-time data will be summarized separately for the Escalation and PK Expansion cohorts, as well as using combined data from both the Dose Escalation and PK Expansion cohorts. For melanoma Expansion cohorts, plasma concentrations of MLN2480 will be summarized by time post-dose and grouped by cohort and dosing cycle and day.

Summary statistics will be reported at scheduled sampling times that have at least 2 patients in the PK evaluable population and the number of observations above the lower limit of quantitation (NALQ) is $\geq 50\%$ of the number of patients. The summary statistics will consist of: N, arithmetic mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean, and NALQ. Arithmetic mean, geometric mean, median, minimum, and maximum will be reported when there are at least 2 non-missing values, while the SD and CV will be reported when there are at least 3 non-missing values. For ease of presentation, scheduled sampling times will be used to present results in summary tables and figures.

Concentrations that are below level of quantification (BLQ) will be set to zero for calculation of summary statistics, except for geometric means, where BLQ values will be excluded. Arithmetic mean, geometric mean, median, minimum and maximum values less than the lower limit of quantitation (LLOQ) will be displayed as BLQ in concentration summaries.

Concentration data that are considered anomalous may be excluded from the concentration summaries and plots. Evidence or explanations will be provided in the clinical study report to justify the exclusion of data.

MLN-2480
Statistical Analysis Plan, Study C28001

For Dose Escalation and PK Expansion cohorts, population mean and individual plasma concentration-time data will be plotted by dose group and dosing cycle and day on linear and semi-logarithmic scales. Population mean and individual trough plasma concentration-time data will be plotted by dose group on a linear scale. Visual inspection of the trough plasma concentration-time plots will be used to make inferences regarding the attainment of PK steady-state. If the same dose is administered in a Dose Escalation and the PK Expansion cohort, the plasma concentration-time data will be plotted separately for the Escalation and the PK Expansion cohorts, as well as combined for both the Dose Escalation and PK Expansion cohorts. BLQ values will be plotted as zero on a linear scale and treated as missing on a semi-logarithmic scale.

Individual plasma concentration data, urine concentration data, and urine collection volume will be listed by time point or urine collection interval. Both scheduled and actual sampling times will be presented in the listings.

PK Parameters for MLN2480

The PK evaluable population will be used for the estimation of PK parameters via noncompartmental analysis.

PK parameter determination in the dose escalation and PK expansion cohorts will be based on individual plasma and urine concentrations of MLN2480 collected at pre-specified times prior to and following MLN2480 administration. Actual sampling times will be used for the calculation of PK parameters. In the event that actual sampling times are either unreliable or missing, scheduled sampling times will be used.

For calculation of PK parameters, concentrations of MLN2480 that are BLQ will be treated as zero prior to T_{max} , as missing between T_{max} and the time of the last measurable concentration, and as zero after the last measurable concentration. If measurable concentrations are near the LLOQ or imbedded between BLQ concentrations, these values may be excluded at the discretion of the Clinical Pharmacologist.

Concentration data that are considered anomalous will not be used in the calculation of PK parameters. Evidence or explanations will be provided in the CSR to justify the exclusion of data.

MLN-2480
Statistical Analysis Plan, Study C28001

As data permit, the following PK parameters will be calculated for MLN2480 by noncompartmental analysis using Phoenix™ WinNonlin® version 6.2 or higher:

Parameter	Definition	Units
C_{max}	Observed maximum plasma concentration	ng/mL
T_{max}	First time Cmax is observed	hr
λ_z	Terminal disposition phase rate constant	1/hr
$t_{1/2z}$	Terminal disposition phase half-life	hr
C_{trough}	Observed plasma concentration at the end of a dosing interval	ng/mL
AUC _t	Area under the plasma/blood/serum concentration-time curve from time 0 to time of the last quantifiable concentration, using the linear-log trapezoidal method	hr*ng/mL
AUC _{tau}	Area under the plasma concentration-time curve, time 0 to end of dosing interval, estimated using the linear-log trapezoidal method	hr*ng/mL
CL/F	Apparent clearance after extravascular administration, calculated as Dose/AUC _∞ after a single dose and as Dose/AUC _τ after multiple dosing (at steady state)	L/hr
PTR	Peak-trough ratio in the steady state	unitless
R _{ac(AUC)}	Accumulation ratio (based on AUC), calculated as AUC _τ at steady state/AUC _τ after a single dose	unitless
Ae _t	Amount of MLN2480 excreted in the urine, collected from time 0 to time = 8 hours	mg
fe	Fraction of drug excreted in urine, calculated as (Ae _t /dose)×100.	%
CL _R	Renal clearance, calculated as Ae _t /AUC(0-t)	L/hr

MLN-2480
Statistical Analysis Plan, Study C28001

Different PK parameters will be estimated in the dose escalation and PK expansion cohorts for different dosing cycles and days, as follows:

Cohort(s)	Dosing Cycles and Day	Parameter
Dose Escalation & PK Expansion Cohort	Cycle 1, Day 1	C_{max} T_{max} C_{trough} AUC_{tau}
	Cycle 1, Day 9	C_{trough}
	Cycle 1, Day 15	C_{trough}
	Cycle 1, Day 21	C_{max} T_{max} C_{trough} AUC_t AUC_{tau} CL/F PTR $R_{ac(AUC)}$ Ae_t fe_t CL_R
PK Expansion Cohort Only	Cycle 1, Day 21	λ_z $t_{1/2z}$

To report λ_z and $t_{1/2z}$, the terminal disposition phase data time span must be greater than or equal to 1.5 and R^2_{adj} must be greater than or equal to 0.8. In addition, a minimum of 3 measurable concentrations must be present within the terminal disposition phase.

Cycle 1, Day 1 C_{trough} and AUC_{tau} will not be reported if the time between Cycle 1, Day 1 dosing time and actual sample collection time for the end of dosing interval (trough) plasma sample is less than 40 hr (in the case of Q2D dosing). Cycle 1, Day 1 C_{trough} also will not be reported if the end of dosing interval plasma sample is collected after start of the next dosing interval. Cycle 1, Day 9 C_{trough} will not be reported if the time between Cycle 1, Day 7 dosing time and actual sample collection time for the Cycle 1, Day 9 predose plasma sample is less than 40 hr, or if the Cycle 1, Day 9 predose plasma sample is collected after Cycle 1, Day 9 dosing. Cycle 1, Day 15 C_{trough} will not be reported if the time between Cycle 1, Day 13 dosing time and actual sample collection time for the Cycle 1, Day 15 predose plasma sample is less than 40 hr, or if the Cycle 1, Day 15 predose plasma sample is collected after Cycle 1, Day 15 dosing. Cycle 1, Day 21 C_{trough} will not be reported if the end of dosing interval plasma sample is collected after start of the next dosing interval.

If the time between Cycle 1, Day 21 dosing time and actual sample collection time for the end of dosing interval (trough) plasma sample is less than 40 hr, and steady-state conditions are inferred, the end of dosing interval plasma concentration may be imputed at the discretion of the Clinical Pharmacologist for the purpose of calculating Cycle 1, Day 21 PK parameters (eg, C_{trough} , PTR, and AUC_{tau}) that are dependent on the end of dosing interval plasma concentration. If imputation is performed, the end of dosing interval plasma

MLN-2480
Statistical Analysis Plan, Study C28001

concentration will be set equal to the pre-dose plasma concentration for the same dosing interval.

For the Dose Escalation and PK expansion cohorts, PK parameters will be summarized and grouped by dose group and dosing cycle and day. If the same dose is administered in a Dose Escalation and the PK expansion cohort, PK parameters will be summarized separately for the Escalation and PK expansion cohorts, as well as combined for both the Dose Escalation and PK expansion cohorts. In addition, Cycle 1, Day 21 T_{max} , AUC_{tau} , CL/F , CL_R , fe_t , PTR , $R_{ac}(AUC)$, and $t_{1/2z}$ will be summarized across all patients in the Dose Escalation and PK expansion cohorts., provided no apparent dose-dependency is observed for these PK parameters.

Except for T_{max} , the summary statistics will consist of: N, mean, SD, CV, median, min, max, and geometric mean. The summary statistics for T_{max} will consist of: N, median, min, and max. Summary statistics of parameter data will be reported for doses with at least 2 patients in the PK parameter population and $\geq 50\%$ of patients have available PK parameter values.

Scatter plots will be generated for Cycle 1, Day 1 and Day 21 C_{max} versus dose, Cycle 1, Day 1 and Day 21 AUC_{tau} versus dose.

Individual PK parameter data will be listed.

Provisional Assessment of Dose Proportionality

If data permit, a regression analysis may be used to assess the dose proportionality of Cycle 1, Day 21 AUC_{tau} . If the same dose is administered in a Dose Escalation and the PK Expansion cohort, only the above PK parameters from the escalation cohort will be include in the regression analysis.

Dose proportionality will be assessed using a power model, described by the following equation:

$$\ln(\text{PK parameter/dose}) = \ln(a) + b * \ln(\text{dose}),$$

where a and b are the estimated parameters of the model. The 95% confidence interval of the estimate of b will be provided.

Population PK Analysis

MLN2480 plasma concentration-time data collected in this study, together with data collected from future studies, may contribute to population PK analysis. Patients undergoing serial or sparse PK sampling will contribute to population PK analysis. The objectives of this analysis are to understand potential sources of PK variability, including patient-specific covariates (eg, age, gender, weight, renal and hepatic function), and to enable exploratory analysis of the relationships between PK and pharmacodynamic effects, efficacy, and safety. If applicable, the specifics of the population PK modeling approaches will be described separately in a population PK analysis plan and the results will be reported separately from the CSR.

5.9.2 Pharmacodynamic Analyses

The pharmacodynamic evaluable population will be used for the PD analysis.

MLN-2480
Statistical Analysis Plan, Study C28001

Summary and percent change from baseline of the PD biomarkers will be tabulated with descriptive statistics (N, mean, standard deviation, median, min, and max).

The PD biomarkers in the tumor immunohistochemistry (IHC) will include, but not be limited to the direct pathway marker of Raf inhibition (pERK), proliferation marker (Ki67) and apoptotic marker (Bim-1).

Relationships between response and PD biomarkers may be explored graphically.

The relationship between MLN2480 exposures and tumor PD biomarkers may also be explored.

Individual PD data will be presented in a by-patient listing.

5.9.3 Pharmacogenetics Analyses

Individual patient DNA genotype (BRAF, NRAS, and others) will be listed with clinical response.

If applicable, drug metabolizing enzyme and/or transporter genotypes will be listed by patient. Descriptive statistics and graphical methods may be used to explore the relationship between these genotypes and selected PK parameters of MLN2480.

5.10 Safety Analyses

Safety evaluations will be based on the incidence, intensity, and type of AEs and on clinically significant changes in the patient's vital signs, weight and clinical laboratory results. Safety variables will be tabulated and presented for the safety population. The incidence of DLT will be presented in a listing.

These analyses will be performed using the safety population.

5.10.1 Adverse Events

5.10.1.1 Adverse Events

Adverse events will be coded using MedDRA Version 16.0. All AEs will be presented in a by-patient listing. Treatment-emergent AEs (TEAEs) will be tabulated. A TEAE 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 medication, 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 or is subsequently considered drug-related by the investigator.

Patients with the same AE occurring more than once will have that AE counted only once within each body system, each high level term, and each preferred term. TEAEs will be tabulated by system organ class, high level term and preferred term for the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.

MLN-2480
Statistical Analysis Plan, Study C28001

- The most commonly reported TEAEs (ie, those events reported by $\geq 10\%$ of all patients in the safety population).
- TEAEs by maximum intensity (CTCAE grade).
- Drug-related TEAEs by maximum intensity (CTCAE grade).
- TEAEs resulting in study drug discontinuation.
- TEAEs resulting in study drug dose reduction.

TEAEs will be tabulated by system organ class, preferred term, and highest intensity. Most commonly reported (at least 10% of all subjects) TEAEs will be presented by preferred term only.

AEs will be summarized by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients with the same AE occurring more than once will have the maximum intensity of that AE counted once within each body system, high level term and preferred term.

An overall summary AE table will include numbers and percentages of patients who had any AE, drug-related AE, grade 3 or higher AE, grade 3 or higher drug-related AE, serious AE (SAE), drug-related SAE, AE resulting in treatment discontinuation, AE resulting in dose reduction, AE resulting in dose modification (defined as delay, reduction or discontinuation), and on-study deaths. On-study death is defined as the death that occurs between the first dose of study drug and 30 days of the last dose.

Additionally, by-patient listings of the AE of special interest will be presented including rash or others as appropriate.

5.10.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment-emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high level term, and preferred term. A drug-related SAE summary will also be produced.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent status).

5.10.1.3 Deaths

A by-patient listing of the on-study deaths will be presented. On-study death is defined as the death that occurs between the first dose of study drug and 30 days after the last dose of study drug.

5.10.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of TEAEs resulting in discontinuation of study drug will be presented.

The number and percentage of patients experiencing at least one AE resulting in discontinuation of study drug will be summarized by MedDRA system organ class, high level term, and preferred term.

5.10.1.5 Adverse Events Resulting in Dose Reduction

A by-patient listing of TEAEs resulting in dose reduction of study drug will be presented.

The number and percentage of patients experiencing at least one AE resulting in dose reduction will be summarized by MedDRA system organ class, high level term, and preferred term.

5.10.1.6 Dose Limiting Toxicities (DLTs)

A by-patient listing of DLTs that occur during Cycle 1 of treatment will be presented for patients from dose escalation.

5.10.2 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standard units. If a lab value is reported using a non-numeric 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 non-numeric qualifier. If there are multiple values with the same date at a visit for any patient, the average of those values will be used. If there are multiple values with different dates for the same visit, then the latest value will be used.

Shift tables of the change in National Cancer Institute Common Terminology Criteria for (NCI CTC) for toxicity from baseline to the post baseline worst CTC grade will be generated for relevant parameters. Scatter plots of baseline versus worst post-baseline values will be generated. Parameters to be tabulated will include:

- Hematology: ANC, hemoglobin, platelets, WBC.
- Clinical chemistry: ALT, AST, alkaline phosphatase, creatinine, total bilirubin, calcium, CO₂, potassium, glucose, albumin and sodium.

All hematology and clinical chemistry data will be also presented in by-patient listings, respectively.

5.10.3 Electrocardiograms

For the triplicate 12-lead electrocardiogram (ECG) summaries, the baseline is defined as the average of the triplicate 12-lead ECG measurements recorded at 2 to 5 minute intervals on Cycle 1, Day 1 before dosing (predose).

A summary of ECG abnormalities will be presented by visit. The ECG intervals, including QT, QT adjusted by an appropriate correction (QTcB and QTcF [Bazett and Fridericia]), PR, QRS, and RR, will be summarized at each scheduled time point, along with change from baseline to each post-treatment time point.

$$QTc \text{ (Bazett)} = QT / (RR^{0.5})$$

$$QTc \text{ (Fridericia)} = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

MLN-2480
Statistical Analysis Plan, Study C28001

The number and percent of patients with QTc falling into the following categories: ≤ 450 , $> 450-480$, $> 480-500$, and > 500 msec, will be summarized at each scheduled time point as well as the number and percent of patients with changes from baseline of ≥ 30 msec and ≥ 60 msec. A similar summary will also be presented for maximum QTc (maximum over all time points) using the same categories.

Individual ECG data will be presented in by-patient listings.

In addition, the relationship between MLN2480 plasma concentrations and select ECG parameters (eg, change in QTc from baseline) may be evaluated using data from this and other studies using a population concentration-effect analysis approach. If conducted, this analysis will be reported separately from the CSR.

5.10.4 Vital Signs

The actual values of vital sign parameters, including oral temperature, heart rate, weight and systolic and diastolic blood pressure, will be summarized over time. Summary of change from baseline will also be presented. A by-patient listing will be presented.

5.10.5 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status over time will be summarized. Shifts from baseline to the worst post-baseline over time will be summarized. A by-patient listing will also be presented.

5.10.6 Other Safety Assessments

A listing of DLTs occurring in Cycle 1 will be presented.

A listing of dermatology exam results and percent change from baseline in size will be presented.

Additional safety analyses may be determined at any time without prejudice to enumerate rates of toxicities and to further define the safety profile of study drugs.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

There is no change made to the planned analyses from the protocol.

Reference materials for this statistical plan include Clinical Study Protocol C28001 Amendment 8 (dated 22 July 2015).

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.

Baseline values are defined as in Section 5.4.2.

MLN-2480
Statistical Analysis Plan, Study C28001

Treatment emergent AEs are defined as in Section 5.10.1.1.

8. REFERENCES

1. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

on-commercial use only and subject to the applicable Terms of Use