Title: A Phase 1b Study of Alisertib (MLN8237) in Combination With Weekly Paclitaxel in East Asian Patients With Advanced Solid Tumors

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STATISTICAL ANALYSIS PLAN

A Phase 1/1b Study of Alisertib (MLN8237) in Combination with Weekly Paclitaxel in East Asian Patients with Advanced Solid Tumors

Protocol #: C14022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the plasma concentration versus time curve
$AUC_{0-\tau}$	area under the plasma concentration versus time curve zero to next dose
BID	bis in die; twice a day
BSA	Body surface area
CL_{ss}/F	steady-state apparent oral clearance
C_{max}	maximum plasma concentration
C_{trough}	trough concentration
DLT	dose-limiting toxicity
DSMB	data safety monitoring board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ECT	enteric-coated tablet
G-CSF	granulocyte colony-stimulating factor
IWG	International Working Group
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTC	National Cancer Institute Common Terminology Criteria
NPO	nothing by mouth
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
T_{max}	first time to maximum plasma concentration
UGT	uridine diphosphate glucuronosyltransferase
WBC	white blood cell
WHO	World Health Organization

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 addresses 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 1b study to evaluate the safety, tolerability, and PK of alisertib in combination with weekly paclitaxel in East Asian patients. The study is in 2 parts: the first part is a dose escalation to determine the MTD and define the RP2D of the alisertib plus paclitaxel combination in East Asian patients with advanced solid tumors; the second part is an expansion cohort at the RP2D of the alisertib plus paclitaxel combination in East Asian patients with either OC or SCLC. Alisertib will be administered orally 3 days on/4 days off for 3 weeks on Days 1 through 3, 8 through 10, and 15 through 17 in 28-day cycles. Paclitaxel 60 mg/m^2 IV will be administered on Days 1, 8, and 15 in 28-day cycles. The paclitaxel dose will remain constant throughout the dose escalation and expansion parts of this study. Enrolled patients may receive study drug until observed progression, need of discontinuation because of toxicity, lost to follow-up, study is terminated by the sponsor, protocol violation, unsatisfactory therapeutic response, or voluntary withdrawal by the patient from the study. Patients may discontinue therapy at any time. Patients will attend the End of Treatment visit 30 days after receiving their last dose of study drug.

Up to 3 dose cohorts are planned with 3 to 6 patients enrolled per cohort based on the standard 3+3 dose escalation scheme. Dosing will begin with 15 mg BID, followed by 25 mg as tolerated.

If ≥ 2 of the first 6 patients experience a DLT at 15 mg BID, depending on the overall safety profile, the type of AEs/DLTs observed, and the available PK data, a decision will be made

either to expand the 15 mg BID alisertib cohort with 6 additional patients, or to de-escalate the Alisertib dose to 10 mg BID (DL-1), or to terminate the study.

Once the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) levels are determined, at least 12 patients will be treated at the RP2D to more fully characterize the safety, tolerability, and pharmacokinetics (PK) of alisertib.

1.2 Study Objectives

The primary objectives are:

- To evaluate the safety and tolerability and determine the MTD to subsequently define an RP2D of alisertib in combination with weekly paclitaxel in East Asian patients with advanced solid tumors.

- To characterize the PK of alisertib and paclitaxel in the combination setting in East Asian patients with advanced solid tumors.

The secondary objective is:

- To identify initial signs of antitumor activity in patients with relapsed/refractory OC or SCLC.

2. POPULATIONS FOR ANALYSIS

2.1 Safety Population

The safety population will include all patients who receive at least 1 dose of alisertib. The safety population will be used for all safety analyses.

2.2 Pharmacokinetics Population

The PK population, defined as all patients who have sufficient dosing data and plasma concentration-time data to permit calculations of PK parameters, will be used for PK analyses.

PK analyses will be performed using the PK population.

2.3 DLT-evaluable Population

The DLT-evaluable population, defined as all patients who either experience DLT during Cycle 1 or complete treatment with at least 15 of the planned 18 doses of alisertib and 2 of the planned 3 doses of paclitaxel in Cycle 1 unless AE/DLTs and have 28-day follow up data in Cycle 1 to allow the investigators and sponsor to determine whether DLT occurred, will be used for analysis of DLT.

The DLT-evaluable population will be used for the analysis of DLT and MTD.

3. HYPOTHESES AND DECISION RULES

No formal statistical hypothesis or decision rule is planned.

4. INTERIM ANALYSIS

4.1 Interim Analysis

No interim analysis is planned. Data will be reviewed on a continuous basis.

4.2 Data Safety Monitoring Board (DSMB)

There is no IDMC/DSMB in this study.

5. STATISTICAL METHODOLOGY

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

5.1 Sample Size Justification

Up to 3 dose cohorts are planned with 3 to 6 patients enrolled per cohort based on the standard 3+3 dose escalation scheme. Once the MTD and RP2D levels are determined, at least 12 patients additional patients will be treated at the RP2D to more fully characterize the safety, tolerability, and PK of alisertib. Assuming 10% of patients are not evaluable for DLT, PK or both, it is anticipated that enrollment of approximately 30 patients is needed.

5.2 Randomization and Stratification

Randomization will not be used in this study.

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. Every effort will be made to avoid missing/partial date in on-study data.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

5.4.1.1 Missing/Partial Dates in Adverse Events

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

- If the start date has month and year but day is missing, the event will be considered treatment emergent if 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 study drug,

      and

    - On or before the month and year of (the date of the last dose of study drug plus 30 days).
- If the start date has year, but 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 study,

      and

    - On or before the year of (the date of the last dose of study plus 30 days).
- If the start date of an event is completely missing then the event is assumed to be treatment emergent.

However, if the end date is complete or partially missing but it is clear that the end date is before the first dose of study drug, the event will not be considered treatment emergent.

5.4.1.2 Missing/Partial Dates in Concomitant Medications

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

- If the start date has month and year but day is missing, the event will be considered concomitant if 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 study drug,

  and

- On or before the month and year of (the date of the last dose of study drug plus 30 days).

- If the start date has year, but day and month are missing, the event will be considered concomitant if the year of the start date of the event is:

  - On or after the year of the date of the first dose of study,

    and

  - On or before the year of (the date of the last dose of study plus 30 days).

- If the start date of an event is completely missing then the event is assumed to be concomitant.

However, if the end date is complete or partially missing but it is clear that the end date is before the first dose of study drug, the event will not be considered concomitant.

When the start date is complete and is before the first dose, and the concomitant medication is not ongoing but the end date is missing completely or partially, similar algorithm should be used to assess whether end date is before last dose of study plus 30 days to be included.

5.4.1.3 Missing Data in PK Analyses

For AUC calculation in PK analyses, the pre-dose concentration in an individual following multiple dose administration may be used in place of the concentration at the end of the dosing interval (or vice versa) if one of these data points is not available and scientific considerations based on PK characteristics of alisertib support conclusion of achievement of steady-state on the day of PK sampling.

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.

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.

5.4.5 Withdrawals, Dropouts, Lost to Follow-up

Patients will be replaced if they are not evaluable for DLTs. These additional patients will receive the same allocation of treatment as those for whom they replaced.

5.5 Patient Disposition

A disposition of patients includes the number and percentage of patients for the following categories by the dose level the patient is enrolled to and total: patients in the safety population, patients in the PK population, patients in the DLT-evaluable population, and patients discontinued from the study. 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.

A listing will present data concerning patient disposition.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Demographic and baseline characteristics will be summarized by the dose level the patient is enrolled to and total. Baseline demographic data to be evaluated will include age, gender,

race, ethnicity, country, height, weight, and body surface area (BSA). Demographic data will also be presented in a by-patient listing.

The formulation for BSA is:

BSA = sqrt(height(cm) x weight (kg) / 3600),

where weight is in kilograms and height in meters.

5.6.2 Medical History

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

5.6.3 Baseline Disease Status

Baseline disease type will be summarized by the number and percentage of patients in the safety population, presented by the dose level the patient is enrolled to and total. Eastern Cooperative Oncology Group (ECOG) performance status will be summarized similarly in the same table. Separate by-patient listings will also be presented for baseline disease type and ECOG performance status.

A separate by-patient listings may be presented for prior therapy, prior surgery, and prior radiation, pending data availability.

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded by preferred term using the 2014 March version of the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from 28 days before the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first, will be tabulated by WHO drug generic term, presented by the dose level the patient is enrolled to and total. Patients are counted once for

each 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

Alisertib will be administered orally 3 days on/4 days off for 3 weeks on Days 1 through 3, 8 through 10, and 15 through 17 in 28-day cycles. Alisertib dosing during Cycle 1 will begin at Cycle 1, Day 1, the same day as the first dose of paclitaxel; alisertib will be administered 1 hour before the start of the paclitaxel infusion. In Cycle 2, alisertib doses will be held on Days 1 through 3. During the dose escalation and expansion part, for Cycle 2 only, patients will receive 12 doses of alisertib, administered BID on Days 8 through 10 and 15 through 17 to permit PK assessment of paclitaxel alone up to 48 hours. Alisertib dosing in all subsequent cycles (Cycle 3 and beyond) will begin on Day 1. Paclitaxel 60 mg/m^2 IV will be administered on Days 1, 8, and 15 in 28-day cycles. The paclitaxel dose will remain constant throughout the dose escalation and expansion parts of this study.

5.7.2.1 Extent of Exposure

The exposure to alisertib will be characterized by total amount of dose taken in mg, total number of dose taken, number of treated cycles for alisertib, numbers and percentages of patients who had ≥1, ≥2, …, and ≥6 treated cycles for alisertib and relative dose intensity The exposure to paclitaxel will be characterized by total amount of dose taken in both mg and mg/m^2, total number of dose taken, number of treated cycles for paclitaxel, numbers and percentages of patients who had ≥1, ≥2, …, and ≥6 treated cycles paclitaxel and relative dose intensity A treated cycle is defined as a cycle in which the patient received any amount of specified study drug.

Relative dose intensity (%) for alisertib is defined as 100×(total amount of dose taken (mg))/ (prescribed dose per day*planned treated days.

Relative dose intensity (%) for paclitaxel is defined as 100×(total amount of dose taken (mg/m^2))/(prescribed dose per day*planned treated days).

Prescribed dose is determined by the dose level to which a patient is enrolled at the onset of the study.

Dosing data will also be presented in a by-patient listing.

5.7.2.2 Treatment Modifications

Action on study drug will be summarized for each of the Cycle 1 through 6, sum of the remainder Cycles, and total, by the dose level the patient is enrolled to and total.

5.8 Efficacy Analyses

All efficacy evaluations will be conducted using the safety population. There is no primary efficacy endpoint in the study. The secondary efficacy endpoint in the expansion part of the study is the disease response based on the RECIST version 1.1 ORR (CR + PR), which will be presented in a listing.

Tumor measurements, if collected, will be presented in by-patient listings.

5.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

5.9.1 Pharmacokinetic Analyses

Paclitaxel

Individual and mean plasma concentration data (grouped by alisertib dose level) will be plotted over time for paclitaxel alone (Cycle 2, Day 1) and for paclitaxel administered concomitantly with alisertib (Cycle 1, Day 1). Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters, including, but not limited to, C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, and $t_{½}$, for paclitaxel administered alone (Cycle 2, Day 1) and during concomitant administration of alisertib (Cycle 1, Day 1).

Descriptive statistics will be presented for plasma PK parameters grouped by alisertib dose level. Additionally, the ratio of geometric means of paclitaxel C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}inf}$ (when administered with the MTD/RP2D of alisertib in reference to when administered alone) and the associated 90% CI will be calculated..

Alisertib

Individual and mean plasma concentration-time data will be plotted for alisertib on Days 1 and 3 by dose level. Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters of alisertib, including but not limited to, Day 1 and Day 3 C_{max}, T_{max}, and $AUC_{0-\tau}$. Alisertib plasma concentration-time data and PK parameters will be summarized descriptively by dose level using the PK-evaluable population.

5.9.2 Pharmacodynamic Analysis

This is not applicable to this study.

5.9.3 Biomarkers

This is not applicable to this study.

5.10 Safety Analyses

Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes, vital signs, weight, and clinical laboratory results.

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 18.0 or higher. All AEs will be presented in a by-patient listing. Treatment-emergent AEs will be tabulated where treatment-emergent is defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of any study drug, or until the start of subsequent antineoplastic therapy, whichever occurs first. Treatment-emergent AEs will be tabulated according to the MedDRA by system organ class, high level terms and preferred terms and will include the following categories. Patients with 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.

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.

Drug-related treatment-emergent AEs will also be summarized by the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.03 AE intensity. Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, once within each high level term, and once within each preferred term.

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients in the safety population) will be tabulated by system organ class and preferred term. Patients with the same AE more than once will have that event counted only once within each system organ class and once within each preferred term.

The overall treatment-emergent AE summary, Grade 3 or higher treatment-emergent AE, drug-related treatment-emergent AE, and most common treatment-emergent AE will be summarized by the dose level the patient is enrolled to and total.

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. Drug-related SAE will be summarized similarly.

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

5.10.1.3 Deaths

A by-patient listing of the deaths will be presented. All deaths occurring on-study will be displayed (regardless of treatment-emergent AE status). On-study death is defined as the death that occurs between the first dose of study drug and 30 days of the last dose of study drug, or until the start of subsequent antineoplastic therapy, whichever occurs first.

5.10.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-subject listing of AEs resulting in discontinuation of study drug will be presented. All AEs resulting in discontinuation of study drug occurring on-study will be displayed (regardless of treatment emergent AE status).

5.10.1.5 Dose-limiting Toxicities

A by-subject listing of DLTs will be presented.

5.10.2 Laboratory Data

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

Laboratory test results (and/or change from baseline in clinical laboratory parameters) will be summarized according to the scheduled sample collection time point. Unscheduled laboratory test results will only be listed and included in laboratory shift tables.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTC for toxicity (version 4.0) from baseline to post baseline worst CTC grade. Parameters to be tabulated will include:

- Hematology: hemoglobin, platelets, neutrophils, lymphocytes, leukocytes.

- Clinical chemistry: ALT, AST, alkaline phosphatase, creatinine, total bilirubin, calcium, magnesium, potassium, albumin, and sodium.

Laboratory-related tables will be presented by the dose level the patient is enrolled to and total.

By-patient listings to be presented include hematology and clinical chemistry.

5.10.3 Electrocardiograms

ECG will be presented in a by-patient listing.

5.10.4 Vital Signs

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point through Cycle 6. Vital sign tables will be presented by the dose level the patient is enrolled to and total.

5.10.5 Other Safety Assessments

Pregnancy testing results will be presented in a by-patient listing.

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. SIGNIFICANT PROTOCOL DEVIATIONS

A listing will be generated for major protocol deviations, which will include, but not limited to, at least one of the following:

- Violation of inclusion/exclusion criteria.

- Use of the following prohibited medications while on study: G-CSF use in Cycle 1, proton pump inhibitors, and H2-receptor antagonists.

- Took less than 75% of expected study drug in a cycle and the cycle length was greater than 35 days; any overdose.

7. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

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

8. PROGRAMMING CONSIDERATIONS

8.1 Statistical Software

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

8.2 Rules and Definitions

Subject populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

Treatment-emergent AEs are defined in Section 5.10.1.1.

9. REFERENCES

Not applicable.