Title: A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A-Mediated Inhibition on the Pharmacokinetics, Safety, and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

NCT Number: NCT02122770

SAP Approve Date: 31 August 2017

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- Named persons or organizations associated with the study.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C15011

A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A-Mediated Inhibition on the Pharmacokinetics, Safety, and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

PHASE 1

Version**:** Final

Date**:** 31 August 2017

Prepared by:

PPD

Based on:

Protocol Version: Protocol Amendment No. 02

Protocol Date: 12 April 2017

1.1 APPROVAL SIGNATURES

Study Title: A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A-Mediated Inhibition on the Pharmacokinetics, Safety, and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

Approvals:

PPD	Date
PPD	Date
PPD	Date
PPD	Date
PPD	Date

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE(s)	adverse event (or events)
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
ANOVA	Analysis of Variance
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
AUEC	area under the effect-time curve
AUEC_Above_24	area of the effect-time curve above baseline (positive value) from 0 to 24 hours post-dose
AUEC_Net_24	sum of the area of the effect-time curve above baseline (positive value) and the area of the effect-time curve below baseline (negative value) from 0 to 24 hours post-dose
AUMC	area under the first moment curve
BSA	body surface area
CKD-epi	chronic kidney disease epidemiology collaboration
CL_p	Systemic clearance
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
Cr	creatinine
CR	complete response
CRF	Case Report Form
CRP	C-reactive protein
CV	coefficient of variation
DBP	diastolic blood pressure
DDI	drug-drug interaction
DIC	disseminated intravascular coagulation
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E_{Max}	observed maximum effect
EOS	End of Study
GFR	glomerular filtration rate
HLT	high level term
IV	intravenous
$lambda_z$	terminal disposition phase rate constant
LLQ	limit of quantification
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities

MRT	mean residence time
MTD	maximum tolerated dose
NAE	Nedd8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	progressive disease
PK	pharmacokinetic
PR	partial response
PT	preferred term
PT	prothrombin time
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SD	stable disease
SOC	system organ class
$t_{1/2}$	terminal disposition phase half-life
TAD	time after dosing
TEmax	time to Emax
T_{max}	first time at which C_{max} occurs
TPR	Ratio of Day 8 pre-dose concentration to Day 8 C_{max}
Vss	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is:

- To assess the effect of multiple-dose administration of fluconazole, a moderate CYP3A inhibitor, on the single-dose IV PK of MLN4924
- To assess the effect of multiple-dose administration of itraconazole, a strong CYP3A inhibitor, on the single-dose IV PK of MLN4924

4.2 Secondary Objectives

The secondary objectives for Part A are:

- To further evaluate the safety and tolerability of MLN4924
- To further describe the IV PK of MLN4924 before and after multiple oral dosing with fluconazole or itraconazole

The secondary objectives for Part B are:

- To further assess the safety and tolerability of MLN4924 in combination with docetaxel in patients with solid tumors
- To further assess the safety and tolerability of MLN4924 in combination with carboplatin and paclitaxel in patients with solid tumors
- To further evaluate disease response that may be observed with the combination of MLN4924 and docetaxel
- To further evaluate disease response that may be observed with the combination of MLN4924, carboplatin, and paclitaxel

4.3 Exploratory Objectives

The exploratory objective for Part A is:

CCI

4.4 Study Design

This study is an open-label, multicenter, parallel group, 2-arm, phase 1 study of MLN4924 designed to assess DDIs with the moderate and strong CYP3A inhibitors fluconazole and itraconazole, respectively. The patient population will consist of patients 18 years of age or older who have a histologically or cytologically confirmed metastatic or locally advanced solid tumor that is deemed appropriate for treatment with 1 of the 2 combination therapies in Part B of this study, or who have progressed despite standard therapy, or for whom conventional therapy is not considered effective.

It is expected that approximately 52 patients will be enrolled in this study to reach the intended total number of PK-evaluable patients in each arm/cohort. In the Fluconazole Arm, approximately 12 PK-evaluable patients will be enrolled. In the Itraconazole Arms, approximately 12 PK-evaluable patients will be enrolled in the 8-mg/m^2 and 20-mg/m^2 MLN4924 cohorts, and 3 additional PK-evaluable patients will be needed in the safety lead-in cohort (15-mg/m^2). Once enrolled into the study, patients will begin treatment in Part A of the study. In Part A, patients will be administered MLN4924 via a 1-hour (± 5 minutes) IV infusion in combination with either fluconazole or itraconazole as indicated below. Once patients complete Part A (including the washout period), they can begin treatment in Part B of the study. In Part B, patients will be administered MLN4924 via a 1-hour (± 5 minutes) IV infusion in combination with either docetaxel or carboplatin + paclitaxel.

Part A: Drug-drug Interaction Assessment

MLN4924 + Fluconazole: Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This low dose of MLN4924 is anticipated to provide an adequate safety margin for DDI assessment. Patients will receive concomitant oral fluconazole at a starting dose of 400 mg on Day 4 and then 200 mg QD on Days 5 through 10. Pharmacokinetic samples will be taken after the MLN4924 dose on Day 1 and after the Day 8 dose of MLN4924 with fluconazole at predetermined time points (up to 72 hours after dosing) to assess the effect of fluconazole on the PK of MLN4924. Additional samples for determination of MLN4924 concentrations in whole blood will be collected on Day 1 only.

MLN4924 + Itraconazole: Patients will receive a single dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8 (see dose cohorts below). Patients will receive concomitant oral itraconazole at a dose of 200 mg QD on Days 4 through 10. Pharmacokinetic samples will be taken after the MLN4924 dose on Day 1 and after the Day 8 dose of MLN4924 with itraconazole at predetermined time points (up to 72 hours after dosing) to assess the effect of itraconazole on the PK of MLN4924. Additional samples for determination of MLN4924 concentrations in whole blood will be collected on Day 1 only. The following dose cohorts will be enrolled sequentially within the Itraconazole Arm:

- Itraconazole Arm, 8-mg/m^2 MLN4924 Cohort: Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This low dose of MLN4924 is anticipated to provide an adequate safety margin for DDI assessment.
- Itraconazole Arm, Safety Lead-in 15-mg/m^2 MLN4924 Cohort: Patients will receive a single 15-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This safety lead-in cohort will confirm the safety margin is adequate before any patients are enrolled in the 20-mg/m^2 MLN4924 Cohort.
- Itraconazole Arm, 20-mg/m^2 MLN4924 Cohort: Patients will receive a single 20-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This dose of MLN4924 falls within the clinically relevant dose range currently evaluated in Phase 1b combination studies of MLN4924 plus standard of care.

A preliminary PK analysis will be conducted after the first 4 to 8 patients have completed the Fluconazole Arm of Part A. After review of the emerging data from the Fluconazole Arm, patient assignment to the Itraconazole Arm will be initiated. Dose modifications of MLN4924 in the Itraconazole Arm may be reconsidered based on the magnitude of the interaction with the moderate CYP3A inhibitor fluconazole and the ability to accurately estimate PK parameters for DDI evaluation.

Following completion of the first 3 patients in the Itraconazole Arm 8-mg/m2 MLN4924 Cohort, preliminary PK data will be reviewed to guide expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients. If these emerging preliminary PK data indicate that the magnitude of the interaction with the strong CYP3A inhibitor itraconazole reaches the anticipated approximately 10-fold change, and individual drug exposures do not exceed those seen at doses of MLN4924 $\geq$ 110 mg/m^2, then up to 3 additional patients to provide 4 to 6 PK-evaluable patients will be enrolled. If the magnitude of the interaction with the strong CYP3A inhibitor itraconazole is much greater than anticipated (greater than the predefined safety margin of 14-fold), with individual MLN4924 exposures exceeding those seen at doses of MLN4924 $\geq$ 110 mg/m^2, then no additional patients will be enrolled in the Itraconazole Arm of Part A.

As of the implementation of Protocol Amendment 1, following completion of Part A by 3 PK-evaluable patients in the Safety Lead-in 15-mg/m2 MLN4924 Cohort, safety and PK data will be reviewed to inform expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients in the 20-mg/m^2 MLN4924 Cohort. If the preliminary PK data from the safety lead-in cohort indicate that the magnitude of the interaction between the proposed 20-mg/m^2 MLN4924 dose and the strong CYP3A inhibitor itraconazole would be greater than the predefined safety margin (5-fold, with individual MLN4924 exposures potentially exceeding those seen at doses of MLN4924 $\geq$110 mg/m^2), then no patients will be enrolled in the 20-mg/m^2 MLN4924 Cohort. Dosing with intermediate doses of MLN4924 and/or evaluation of the drug interaction with the moderate CYP3A inhibitor, fluconazole, may then be reconsidered if it is deemed necessary to further enhance our understanding of the effect of CYP3A inhibition on the PK of MLN4924.

Patients will be required to visit the clinic on Day 4 for their first dose of fluconazole or itraconazole. For both the Fluconazole and Itraconazole Arms, all doses of fluconazole and itraconazole will be administered on an empty stomach with the patient fasting from food and fluids, except water and prescribed medications, for 2 hours before and 1 hour after each dose. Patients are encouraged to take fluconazole or itraconazole doses at approximately the same time each morning and approximately 24 hours apart. On Day 8, patients will take fluconazole or itraconazole together with MLN4924 in the morning at the clinic.

In addition to blood sampling for PK, blood samples in the 24-hour postdose window of each arm following dosing on Day 1 and Day 8 will be collected to measure pharmacodynamic effects of MLN4924. These data will be pooled with data from other MLN4924 clinical studies to contribute to an integrated PK-pharmacodynamic analysis across the program.

Part B: Continued Treatment With MLN4924 in Combination With Standard of Care

After patients complete Part A, they will have the opportunity to continue in the study by participating in Part B. In Part B, patients will receive MLN4924 in combination with either docetaxel or carboplatin + paclitaxel at a dose regimen informed from Study C15010 that has been deemed tolerable (eg, no DLTs in 3 patients or no more than 1 DLT in 6 patients). The selected dose of MLN4924 may be adjusted based on information obtained from the ongoing review of safety data. Safety and disease assessments will be conducted in Part B of the study.

Study drug will be discontinued if a patient experiences study drug-related toxicities. Patients may discontinue therapy at any time. Patients will attend the End-of-Study (EOS) visit 30 days after receiving their last dose of study drug.

Throughout the study in Parts A and B, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and adverse events (AEs) will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained and assessed.

Computed tomography (CT) scans with IV contrast of the chest, abdomen, and pelvis will be performed as entry criteria for Part B (after completing of Part A), along with a clinical reassessment. In addition, in Part B, CT scans with IV contrast encompassing the known sites of disease will be performed at every other cycle and at the EOS visit. If CT scan does not provide adequate imaging, magnetic resonance imaging (MRI) may be used to evaluate sites of disease. Tumor response will be assessed by the investigator at these times using the RECIST criteria, version 1.1.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- Ratio of geometric mean, C_{max}, AUC from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-}tlast}$), and AUC from time zero to infinity ($AUC_{0\text{-}inf}$) of MLN4924 administered with fluconazole versus MLN4924 administered alone and 90% confidence intervals (CIs)
- Ratio of geometric mean, C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}inf}$ of MLN4924 administered with itraconazole versus MLN4924 administered alone and 90% CI

5.2 Secondary Endpoints

The secondary endpoints for Part A are:

- AEs, serious adverse events (SAEs), assessments of clinical and laboratory values, weight and vital signs measurements
- Pharmacokinetic parameters including but not limited to CL, first time to achieve maximum observed plasma concentration (T_{max}), V_{ss}, $t_{1/2}$, and B/P ratio of MLN4924

The secondary endpoints for Part B are:

- AEs, SAEs, assessments of clinical and laboratory values, weight and vital signs measurements
- Measures of disease response including objective response rate and duration of response based on investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1)

5.3 Exploratory Endpoints

The exploratory endpoint for Part A is:

CCI [redacted]

6.0 DETERMINATION OF SAMPLE SIZE

It is anticipated that as many as approximately 52 patients will be enrolled in this study.

The sample size calculation is based on the expected 2-sided 90% CI for the difference in the paired, log transformed AUC (or C_{max}) means of MLN4924 on Day 1 (MLN4924 alone) and Day 8 (MLN4924 co-administered with CYP3A inhibitor). Based on the PK information obtained from Schedules B and C of Study C15001, the within-subject CV was estimated to be 0.12 for AUC and 0.17 for C_{max}, respectively. Assuming that the AUC (or C_{max}) ratio in the presence of fluconazole versus in the absence of fluconazole or in the presence of itraconazole versus in the absence of itraconazole is 2.0, with a sample size of 12 evaluable patients per arm, the 90% CI of the ratio of geometric means is expected to be (1.833, 2.182) for AUC and (1.759, 2.274) for C_{max} based on the above discussed variance assumptions. If the geometric mean AUC (or C_{max}) ratio is X, the corresponding 90% CI is expected to be (1.833X/2, 2.182X/2) (or [1.759X/2, 2.274X/2]).

In the Fluconazole Arm, approximately 12 PK-evaluable patients will be enrolled. In the Itraconazole Arm, approximately 12 PK-evaluable patients will be enrolled in the 8-mg/m^2 and 20-mg/m^2 MLN4924 cohorts, and 3 additional PK-evaluable patients will be needed in the safety lead-in cohort. A patient is PK-evaluable if he or she completes the protocol-specified dosing and PK assessments without dose reductions in Part A. Patients who are not PK-evaluable (see Section 7.2.2) will be replaced. Assuming 25% of the enrolled patients will not be PK-evaluable, approximately 52 patients will be enrolled to provide the total intended number of PK-evaluable patients in each arm of Part A.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.2.

In general, summary tabulations will include the number of observations, (arithmetic) mean, standard deviation (SD), geometric mean and coefficient of variation (%CV) for PK related parameters, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, unless specified otherwise.

Descriptive statistics will be presented with the same precision as the original data. The PK parameters will be summarized with a precision of 3 significant digits, while t_{max} is presented with the number of relevant decimal places to specify the sampling time. Percent CV and frequency percentages will be presented as integers.

Summary statistics will be calculated by time point, if applicable.

7.1.1 Randomization and Stratification

There is no randomization in this study. Patient assignment in Part A and Part B will proceed as below:

Part A: The first 4 to 8 patients will be assigned to the Fluconazole Arm (moderate CYP3A inhibitor). After review of the emerging data (see interim analyses section), the investigator will recommend each patient to the Fluconazole Arm (MLN4924 + fluconazole) or the Itraconazole Arm (MLN4924 + itraconazole), and the patient will be assigned to the appropriate arm by the sponsor based on slot availability until enrollment in each arm is filled.

Part B: Investigators may assign each patient to 1 of the 2 combination regimens (MLN4924 + docetaxel or MLN4924 + carboplatin + paclitaxel) in Part B based on their medical judgment after a washout period of at least 2 weeks (and up to 8 weeks) from the last dose of fluconazole or itraconazole to allow patients to recover from any safety concerns and to confirm that the patient is eligible to participate in Part B.

7.1.2 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.

MLN4924 concentration values missing the corresponding sampling date and time records will be excluded from PK analysis.

7.1.2.1 Missing/Partial Dates in Screening Visit

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

- 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.
- If only a 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 date of the first of January will be used, unless other data indicate that the date is earlier.
- If only a 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.

7.1.2.2 Missing/Partial Dates in Subsequent Therapies

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

1. When month and year are present and the day is missing,
    a. If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.
    b. If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month will be imputed.
2. When only a year is present,
    a. If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
    b. If the onset year is not the same as the year of last dose with study drug, the first day of the year will be imputed.
3. If no components of the onset date are present, the date of last dose + 1 will be imputed.

7.1.3 Definitions of Baseline Values

Part A

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 during Part A. For analysis of ECG data, the baseline value is the average of the screening and Part A Day 1 predose value if ECG is

collected at both screening and Part A Day 1 predose. If ECG is collected at only one of these two time points, the baseline value takes the value of the one that is collected.

Part B

Similarly, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration during Part B. Since there is no screening visit for Part B, the baseline value for ECG is also the one collected at the time closest to, but prior to, the start of study drug administration during Part B.

Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. The analysis of PK data and determination of PK parameters will be based on the actual elapsed time postdose relative to the start of first dosing.

Definition of Study Start Date

Study start date is defined as the date of the signing of the informed consent.

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.

Withdrawals, Dropouts, Loss to Follow-up

Patients who are not PK-evaluable will be replaced. Generally no additional patients will be enrolled due to withdrawals, dropouts, or loss to follow-up.

7.2 Analysis Sets

7.2.1 Safety Population

The safety population for Part A is defined as all enrolled patients who receive at least 1 dose of MLN4924 during Part A.

All safety and pharmacodynamic analyses in Part A will be performed using the safety population for Part A.

The safety population for Part B is defined as all patients who continue to Part B and receive at least 1 dose of study drugs during Part B.

All safety analyses in Part B will be performed using the safety population for Part B.

7.2.2 Pharmacokinetic-Evaluable Population

The PK-evaluable population is defined as all enrolled patients who receive all protocol-specified dose regimens within each period during Part A, did not receive any excluded medications throughout the completion of PK sampling, and have sufficient MLN4924 plasma concentration-time data to reliably estimate PK parameters based on noncompartmental analysis

methods. The patients to be included in the PK-evaluable population will be determined by the Takeda Clinical Pharmacologist upon review of the final data.

PK analyses during Part A will be performed using the PK-evaluable population.

7.2.3 Response-Evaluable Population

The response-evaluable population is defined as all patients who receive at least 1 dose of study drug in Part B, have measurable disease as entry criteria for Part B, and have at least 1 postbaseline disease assessment.

Response analyses for Part B will be performed using the response-evaluable population.

7.3 Disposition of Subjects

Separate tabulations of patient disposition data will be generated for Part A and Part B.

A tabulation of patient disposition data by the DDI cohort (fluconazole and itraconazole treatment arms) and the Part A total for Part A will include the number of patients for the following categories: patients treated (safety population for Part A) during Part A, patients in the PK-evaluable population, patients completing Part A, patients who discontinued study treatment during Part A (including the washout period), the primary reason off study treatment during Part A (including the washout period). Patients will be considered to have completed Part A if they have completed the protocol-specified assessments within Part A of the protocol. Percentages will be based on the number of patients in the safety populations for Part A.

A tabulation of patient disposition data by treatment arm and the Part B total for Part B will also be generated to include the following categories: patients treated (safety population for Part B) in Part B, patients in the response-evaluable population for Part B, patients completing Part B, patients who discontinue study treatment from Part B, and the primary reason off study treatment during Part B. Patients will be considered to have completed Part B of the study if they discontinue treatment during Part B for any of the following reasons:

- Adverse event
- Lost to follow-up
- Progressive disease
- Protocol violation
- Study terminated by sponsor
- Symptomatic deterioration
- Unsatisfactory therapeutic response
- Withdrawal by subject
- Other

Percentages in the table of disposition data for Part B will be based on the number of patients in the safety populations for Part B

Data concerning patient disposition (eg, primary reason off study treatment, patient population) will be presented in by-patient listings.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Demographics

Demographics will be summarized by DDI cohort and total for the safety population in Part A, and by treatment arm and total for the safety population in Part B. Demographic data to be evaluated will include age at date of informed consent, sex, ethnicity, race, height, weight and body surface area (BSA).

BSA is calculated for each patient using the following formula:

BSA = $$\sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

Both Part A and Part B use Height collected at screening. Part A uses weight collected at screening. If a weight at screening is not available, the Part A Day 1 predose weight can be used. Part B uses weight collected at the visit closest, but prior to the Part B Cycle 1 Day 1 study drug administration.

No inferential statistics will be generated.

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

7.4.1 Inclusion/Exclusion Criteria

All inclusion/exclusion information on enrolled patients will be included in a by-patient listing for Part A. Eligibility criteria for dosing during Part B for patients who continue into Part B will be presented in a separate listing. These listings will include whether all criteria were satisfied. For patients who did not satisfy the criteria, the criteria number will be listed with the deviation.

In addition, all protocol deviations will be reviewed, and major protocol deviations will be identified and summarized by Part A and Part B in a table. Any enrolled patients who did not meet inclusion or exclusion criteria will be summarized under the category “Not meeting study inclusion/exclusion criteria”.

Patient pregnancy test results will be included in a separate by-patient listing.

7.4.2 Baseline Disease Status

Baseline disease characteristics (disease type, disease stage, sites of involvement, time since initial diagnosis) will be summarized by DDI cohort and total for the safety population in Part A, and by treatment arm and total for the safety population in Part B, if applicable. ECOG performance status will be summarized similarly in the same table. Separate by-patient listings

will also be presented by Part A and Part B for baseline disease characteristics and ECOG performance status.

Dates of initial diagnosis which are partially missing will be imputed as follows:

- If the date of initial diagnosis has a month and year but the day is missing, the 15th will be inserted as the day.
- If the date of initial diagnosis has a year but the month and the day are missing, June 30th will be inserted.

7.5 Medical History and Concurrent Medical Conditions

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

7.6 Medication History and Concomitant Medications

No summary for medication history.

All concomitant medications will be mapped to generic terms according to the World Health Organization (WHO) drug dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term, presented by DDI cohort and total for the safety population in Part A, and by treatment arm and total for the safety population in Part B. Patients are counted once for each WHO drug generic term. Concomitant procedures will not be coded.

Concomitant medication for Part A is defined as any medication that occurs after administration of the first dose of study treatment during Part A and up through 30 days after the last dose of study drug during Part A for patients who do not continue into Part B or up through Part B C1D1 (predose) for patients who continue into Part B.

Concomitant medication for Part B is defined as any medication that occurs after administration of the first dose of study treatment during Part B and up through 30 days after the last dose of study drug during Part B.

Concomitant therapies with start or end dates that are completely or partially missing will be analyzed using the same imputation rules as adverse events.

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

7.6.1 PriorTherapies

Information on prior therapies will be summarized by DDI cohort and total for the safety population in Part A, and by treatment arm and total for the safety population in Part B. Summarized information on prior therapies will include:

- Number of patients with prior chemotherapy
- Months from last dose of prior chemotherapy to first study dose

- Number of patients with prior radiation
- Months from last prior radiation to first study dose
- Number of patients with prior surgery or non-radiation procedures
- Number of patient with prior transplant

If a day of the month is not provided for the date of prior therapy, prior radiation, or prior surgery, then the 15th will be inserted as the day. If neither a day nor month is provided, then June 30th will be inserted.

In addition, prior chemotherapy regimens will be tabulated by treatment arm and total in Part B. A second tabulation will summarize the following:

- Percentage of patients in Arm 1 (MLN4924+Docetaxel) receiving any taxane-containing regimen prior to dosing in C15011
- Percentage of patients in Arm 2 (MLN4924+ Paclitaxel+Carboplatin) receiving any regimen containing a taxane but not a platinum prior to dosing in C15011
- Percentage of patients in Arm 2 (MLN4924+ Paclitaxel+Carboplatin) receiving any regimen containing a platinum but not a taxane prior to dosing in C15011
- Percentage of patients in Arm 2 (MLN4924+ Paclitaxel+Carboplatin) receiving any regimen containing both a platinum and a taxane prior to dosing in C15011

The categories of regimens described above are defined in the following table.

Taxane-containing regimens	BEVACIZUMAB+CARBOPLATIN+PACLITAXEL
	BEVACIZUMAB+CISPLATIN+DOCETAXEL
	BEVACIZUMAB+CISPLATIN+PACLITAXEL
	BEVACIZUMAB+PACLITAXEL
	CAPECITABINE+DOCETAXEL
	CAPECITABINE+PACLITAXEL
	CARBOPLATIN+PACLITAXEL
	CARBOPLATIN+PACLITAXEL+TRASTUZUMAB
	CISPLATIN+DOCETAXEL
	CISPLATIN+DOCETAXEL+FLUOROURACIL
	CISPLATIN+PACLITAXEL
	CYCLOPHOSPHAMIDE+DOCETAXEL
	CYCLOPHOSPHAMIDE+DOCETAXEL+DOXORUBICIN
	CYCLOPHOSPHAMIDE+DOXORUBICIN+PACLITAXEL

	DOCETAXEL (TAXOTERE) DOCETAXEL+DOXORUBICIN DOCETAXEL+FLUOROURACIL DOXORUBICIN+PACLITAXEL FLUOROURACIL+PACLITAXEL GEMCITABINE+PACLITAXEL PACLITAXEL (ABRAXANE FOR INJECTABLE SUSPENSION; APO-PACLITAXEL; ONXOL; TAXOL) PACLITAXEL+TRASTUZUMAB
Regimens containing a taxane but not a platinum	BEVACIZUMAB+PACLITAXEL CAPECITABINE+DOCETAXEL CAPECITABINE+PACLITAXEL CYCLOPHOSPHAMIDE+DOCETAXEL CYCLOPHOSPHAMIDE+DOCETAXEL+DOXORUBICIN CYCLOPHOSPHAMIDE+DOXORUBICIN+PACLITAXEL DOCETAXEL (TAXOTERE) DOCETAXEL+DOXORUBICIN DOCETAXEL+FLUOROURACIL DOXORUBICIN+PACLITAXEL FLUOROURACIL+PACLITAXEL GEMCITABINE+PACLITAXEL PACLITAXEL (ABRAXANE FOR INJECTABLE SUSPENSION; APO-PACLITAXEL; ONXOL; TAXOL) PACLITAXEL+TRASTUZUMAB
Regimens containing a platinum but not a taxane	CAPECITABINE+CISPLATIN CAPECITABINE+CISPLATIN+EPIRUBICIN CAPECITABINE+EPIRUBICIN+OXALIPLATIN CAPECITABINE+OXALIPLATIN CARBOPLATIN (PARAPLATIN-AQ) CARBOPLATIN+ETOPOSIDE

	CARBOPLATIN+FLUOROURACIL CETUXIMAB+CISPLATIN+VINBLASTINE CETUXIMAB+CISPLATIN+VINORELBINE CISPLATIN (PLATINOL) CISPLATIN+EPIRUBICIN+FLUOROURACIL CISPLATIN+ETOPOSIDE CISPLATIN+FLUOROURACIL CISPLATIN+FLUOROURACIL+LEUCOVORIN CALCIUM CISPLATIN+GEMCITABINE CISPLATIN+IRINOTECAN CISPLATIN+PEMETREXED CISPLATIN+VINBLASTINE FLUOROURACIL+LEUCOVORIN CALCIUM+OXALIPLATIN FLUOROURACIL+OXALIPLATIN OXALIPLATIN (ELOXATIN)
Regimens containing both a platinum and a taxane	BEVACIZUMAB+CARBOPLATIN+PACLITAXEL BEVACIZUMAB+CISPLATIN+DOCETAXEL BEVACIZUMAB+CISPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL+TRASTUZUMAB CISPLATIN+DOCETAXEL CISPLATIN+DOCETAXEL+FLUOROURACIL CISPLATIN+PACLITAXEL

7.7 Study Drug Exposure and Compliance

7.7.1 Study Treatments

Part A

During Part A, patients will receive a single dose of MLN4924 given as an IV infusion on Day 1 and Day 8. Patients will receive either concomitant oral fluconazole or itraconazole on Days 4 through 10.

Part B

During Part B, for Arm 1 (MLN4924 + Docetaxel), patients will be administered docetaxel at a dose of 75 mg/m^2 IV over 1 hour on Day 1 of each cycle. After a mandatory approximately 15-minute time out, MLN4924 will be administered IV. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days.

For Arm 2 (MLN4924 + Paclitaxel + Carboplatin), patients will be administered all three drugs on Day 1 of each cycle. Paclitaxel is given first at a dose of 175 mg/m^2 IV over 3 hours followed by carboplatin AUC5 over 30 minutes. After a mandatory approximately 15-minute time out after carboplatin administration, MLN4924 will be administered IV. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days.

All dosing information for each visit will be presented by Part A and Part B in a by-patient listing.

7.7.2 Extent of Exposure

Extent of exposure will be reported separately for Part A by DDI cohort and for Part B by treatment arm.

Part A

The exposure to MLN4924 during Part A will be characterized by the number of doses received, Total Dose Received, Total Dose Expected, and Percent Dosing Intensity.

Percent Dosing Intensity will be calculated using the following equations for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg):

$$\text{Daily Expected Dose} = \text{Dose Level Assigned at Study Entry (mg/m}^2\text{)} * \text{Body Surface Area (m}^2\text{)}$$

$$\text{Daily Prepared Dose} = \text{Scheduled Dose Level (mg/m}^2\text{)} * \text{Body Surface Area (m}^2\text{)}$$

$$\text{Daily Dose Received} = \text{Daily Prepared Dose} * \left(\frac{\text{Volume of IV bag actually infused (mL)}}{\text{Prepared Volume}} \right)$$

The scheduled dose level will be collected on the electronic case report form (eCRF) for each dosing day. Body surface area (BSA) will be calculated on Day 1.

Total Dose Received, Total Dose Expected, and Percent Dosing Intensity for MLN4924 will be based on the following formulas:

$$\text{Total Dose Received} = \text{Sum of Daily Dose Received over all days with MLN4924 administration during Part A}$$

$$\text{Total Dose Expected} = \text{Daily Expected Dose} * 2$$

$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

The extent of exposure to MLN4924 during Part A will be summarized by DDI cohort.

The extent of exposure to fluconazole or itraconazole will be summarized for the number of doses received and Total Dose Received (mg) by DDI cohort.

Part B

The extent of exposure to MLN4924 will be based on the number of cycles received and the mean number of doses administered per cycle. The distribution of the number of cycles received will be presented by treatment arm for all patients treated in Part B. Patients will be considered to have been treated for a cycle if they receive at least one dose of MLN4924 during the 21 days of that cycle. Percentages will be calculated by treatment arm, and total for Part B.

The mean number of doses per cycle will be calculated for each patient and summarized by treatment arm, and total for Part B.

For MLN4924, calculation of Percent Dosing Intensity will use similar equations as specified in Part A for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg). Daily Expected Dose and Daily Prepared Dose may differ if there are dose decreases.

Body surface area (BSA) will be calculated on Cycle 1, Day 1, and at subsequent visits if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

Total Dose Received, Total Dose Expected, and Percent Dosing Intensity for MLN4924 during Part B will be based on the following formulas:

$$\text{Total Dose Received} = \text{Sum of Daily Dose Received on all days with MLN4924 administration in Part B}$$

$$\text{Total Dose Expected} = \text{Daily Expected Dose} * 3 \text{ doses per cycle} * \text{number of treated cycles}$$

$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

Total dose expected will be calculated based on the BSA measured at baseline for Part B. If there are dose increases, the Dosing Intensity may exceed 100%. The number of patients with 100% intensity, 80% - <100%, 50 - <80, and <50% intensity will be summarized by treatment arm, and total for Part B.

For each of the standard of care drugs, the extent of exposure will be summarized in a similar manner as MLN4924. The number of cycles of standard of care drug administered will also be summarized.

The mean number of doses per cycle will be calculated for each patient and summarized by treatment arm, and total for Part B.

Daily Expected Dose, Total Dose Received, Total Dose Expected, and Dosing Intensity for each standard of care drug will be based on the following formulas:

Daily Expected Dose (Docetaxel and Paclitaxel) =

Dose Level Assigned at Study Entry (mg/m^2) * Body Surface Area (m^2)

Daily Expected Dose (Carboplatin) =

Dose Level Assigned AUC at Study Entry (mg x min/mL) * (Glomerular filtration rate (mL/min) +25)

Daily Prepared Dose (Docetaxel and Paclitaxel) =

Scheduled Dose Level (mg/m^2) * Body Surface Area (m^2)

Daily Prepared Dose (Carboplatin) (mg) =

Scheduled Dose Level (AUC) * (Glomerular filtration rate +25)

$$\text{Daily Dose Received} = \text{Daily Prepared Dose} * \left(\frac{\text{Volume of IV bag actually infused (mL)}}{\text{Prepared Volume}} \right)$$

AUC is the area under the free carboplatin plasma concentration versus time curve.

Dosing intensity for each standard of care drug will be summarized by treatment arm, and total for Part B, in a similar manner to MLN4924 dosing intensity.

Dosing administration data for both Part A (including CYP3A inhibitors) and Part B (including SoC) will also be presented in separate by-patient listings.

7.7.2 Treatment Compliance and Modifications

The actions on study drugs (Dose Held, Dose Reduced, Dose Interrupted, Dose Delayed, Dose Missed, Dose Increased, or Discontinued) will be summarized by DDI cohort for the safety population in Part A, and by treatment arm and total in Part B. For Part B, data will be summarized for Cycle 1 only as well as all cycles. A patient will count only once for each type of action.

7.8 Efficacy Analysis (Part B)

Efficacy analysis is only conducted for Part B, where efficacy is not a primary endpoint. A summary of the best overall response as determined by the investigator using the RECIST version 1.1 guidelines will be presented as a measure of antitumor activity of MLN4924 in combination with standard of care drugs. The number and percentage of patients in each disease response category (e.g., complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], overall response rate (CR + PR) and CR+PR+SD) will be presented by treatment arm. Percentages will also be calculated for the total in Part B. All evaluations of response will be conducted using the response-evaluable population.

For each patient, the best percent change (ie, largest reduction) from baseline in the sum of the longest diameter will be calculated and displayed in a waterfall plot to show the distribution of response in each arm. Unscheduled visits will also be included in such displays.

The duration of disease response (CR or PR) will be presented in a by-patient listing for all response-evaluable patients with CR or PR. Duration of response is the time from the date of first documented response per the investigator response assessment to the date of first documentation of PD, or death , or the date of last disease assessment if the patient discontinues treatment before PD or still ongoing. In addition, the date of first response and the date of first documentation of PD after the first response will be shown. The duration of response (in treatment cycle and months), will also be summarized descriptively by treatment arm for all response-evaluable patients.

The duration of SD or better will be presented in a by-patient listing for all response-evaluable patients with SD or better. Duration of SD or better is the time from the date of first documented SD or better to the date of first documentation of PD or death, or the date of last disease assessment if the patient discontinues treatment before PD. In addition, the date of first dose, the date of first SD or better, the date of first documentation of PD, and the number of cycles with SD or better will be shown. The duration of SD or better (in months) and the number of cycles with SD or better will also be summarized descriptively by treatment arm for all response-evaluable patients.

A separate listing will be generated for patients who are on treatment for at least 4 cycles during Part B. This listing should include disease type, number of cycles on treatment, duration of stable disease or better, and prior therapies.

Results from all disease response assessments and whether there was symptomatic deterioration will be presented in by-patient listings.

Any tumor assessments after the alternate antineoplastic therapies or after disease progression will be excluded in the analyses.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis (Part A)

During Part A of the study, for both the Fluconazole and Itraconazole Arms, serial blood samples (approximately 3 mL each) will be collected from each patient for the determination of MLN4924 plasma concentrations before and after the start of MLN4924 infusion on Day 1 (when administered alone) and Day 8 (when co-administered with fluconazole or itraconazole) at the time points indicated below:

Study Day/Time	Day 1	Day 2	Day 3	Day 4	Day 8[a]	Day 9[a]	Day 10[a]	Day 11
Predose[b]	X				X			
End of infusion (EOI) (– 5 to + 1 min)[c,d]	X[e]				X			
0.5 hour postinfusion (± 5 min)[f]	X				X			
1 hour postinfusion (± 15 min)[d,f]	X				X			
2 hours postinfusion (± 15 min)[f]	X[e]				X			
3 hours postinfusion (± 30 min)[d,f]	X				X			
4 hours postinfusion (± 45 min)[f]	X				X			
8 hours postinfusion (± 1 hour)[f]	X[e]				X			
12 hours postinfusion (± 1 hour)	X				X			
24 hours postdose (± 1 hour)[g]		X[e]				X		
48 hours postdose (± 2 hours)[g]			X				X	
72 hours postdose (± 3 hours)[g]				X				X

Abbreviations: ECG = electrocardiogram; IV = intravenous; min = minutes; PK = pharmacokinetic(s).

a Patients should be instructed to come to the clinic in the morning without taking their morning doses of study drug(s). All doses of study drug(s) will be administered on an empty stomach.

b The sample is to be collected within 1 hour before the start of MLN4924 infusion.

c The window for collection of the EOI time point is between 5 minutes before completion of the infusion to 1 minute after completion of the infusion. If the IV infusion is interrupted, 2 additional PK samples (1 sample drawn when the infusion is stopped and 1 sample drawn when the infusion is restarted) should be collected so that the patient may be considered PK evaluable. Please refer to Section 6.1.1 if the IV infusion needs to be interrupted or slowed.

d When the timing of a blood draw coincides with the timing of vital signs or ECG measurements, the vital signs or ECG will be completed before the blood sample collection, with the exception of the EOI sample, which should be collected before the ECG is completed. Full details of PK sample preparation will be provided in the Study Manual.

e Sampling for determination of MLN4924 concentrations in whole blood. Full details of PK sample preparation will be provided in the Study Manual.

f Samples are to be collected after **the completion** of MLN4924 IV infusion.

g Samples are to be collected 24 (± 1 hour), 48 (± 2 hours), and 72 (± 3 hours) hours **after initiation** of the MLN4924 IV infusion on Day 1 (or Day 8).

Additionally, 4 samples for the determination of MLN4924 concentrations in whole blood will be drawn from each patient at pre-specified time points (EOI, 2, 8 and 24 hours) following MLN4924 infusion on Day 1 only.

Individual MLN4924 plasma concentration-time data obtained on Day 1 and Day 8 will be analyzed by noncompartmental methods using WinNonlin version 6.1 (or higher).

The PK analysis population will be used for the description of the concentration-time profiles and for the estimation of PK parameters.

Plasma concentration values below the lower limit of quantification (<LLQ) of the bioanalytical assay will be set to zero for analysis. Actual PK sampling times will be used in the derivation of PK parameters. The exact date and time of each sample collection, as well as the actual start and stop times of the infusion, should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion. Actual time after dosing (TAD) will be set to zero for pre-infusion samples and calculated as the difference between the sample collection date/time and the start date/time of the IV infusion.

The following plasma PK parameters will be estimated, as permitted by the data:

Parameters	Definition	Units
C_{max}	Maximum observed concentration (theoretically end-of-infusion concentration)	ng/mL
T_{max}	First time at which C_{max} occurs	hr
AUC_{last}	Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration	hr*ng/mL
$AUC_{0\text{-}72hr}$	Area under the plasma concentration-time curve from time zero to 72 hours post-dose	hr*ng/mL
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve extrapolated to infinity	hr*ng/mL
$lambda_z$	Terminal disposition phase rate constant	1/hr
$t_{1/2}$	Terminal disposition phase half-life	hr
CL_p	Systemic clearance	L/hr
Vss	Volume of distribution at steady-state	L
TPR	Ratio of Day 8 pre-dose concentration to Day 8 C_{max}	%

To report $lambda_z$, $t_{1/2}$, $AUC_{0\text{-}inf}$, CL_p, and V_{ss}, the terminal disposition phase data time span must be greater than or equal to 2, the number of data points included in the calculation must be at least 3, and R^2 must be greater than or equal to 0.8.

If a subject's predose MLN4924 concentration is ≤ 5% of C_{max} on Day 8, the subject's data without any adjustments will be included in the PK and statistical calculations. If the predose concentration is > 5% of C_{max} on Day 8, the subject will be excluded from PK parameter calculations and summary statistics of concentrations for the given period, and from the statistical comparison of PK parameters.

For assessment of the effect of fluconazole on the single-dose IV PK of MLN4924, the ratios of geometric mean C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}72hr}$, and $AUC_{0\text{-}inf}$ of MLN4924 (in the presence of fluconazole on Day 8 vs in the absence of fluconazole on Day 1) and associated 2-sided 90% CIs will be calculated based on the within-patient variance calculated by ANOVA. Subject will be treated as a random effect in the model. Point estimates and adjusted 90% confidence intervals for the difference in the log ratios will be constructed. The point estimate and adjusted 90% confidence intervals will then be exponentially back transformed to provide point and confidence

interval estimates for the ratios of interest appropriately (eg, C_{max} of MLN4924 with fluconazole vs. C_{max} of MLN4924).

For assessment of the effect of itraconazole on the single-dose IV PK of MLN4924, the ratios of geometric mean C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-72hr}}$, and $AUC_{0\text{-inf}}$ of MLN4924 (in the presence of itraconazole on Day 8 vs in the absence of itraconazole on Day 1) and associated 2-sided 90% CIs will be calculated based on the within-patient variance calculated by ANOVA. Subject will be treated as a random effect in the model. Point estimates and adjusted 90% confidence intervals for the difference in the log ratios will be constructed. The point estimate and adjusted 90% confidence intervals will then be exponentially back transformed to provide point and confidence interval estimates for the ratios of interest appropriately (eg, C_{max} of MLN4924 with itraconazole vs. C_{max} of MLN4924).

Individual MLN4924 plasma concentration-time data (including nominal, actual and elapsed times relative to dosing; TAD) and individual plasma PK parameters will be listed and summarized descriptively on Day 1 and Day 8 by DDI cohort.

Individual MLN4924 whole blood concentration-time data (including nominal, actual and elapsed times relative to dosing; TAD) and individual blood to plasma (B/P) concentration ratios obtained on Day 1 will be listed and summarized descriptively by DDI cohort. The B/P concentration ratio will be calculated as [MLN4924] in blood divided by [MLN4924] in plasma for each of the 4 pre-specified collection times.

Summary statistics (N, arithmetic mean, standard deviation, geometric mean, coefficient of variation [CV], median, minimum, and maximum) will be calculated if there is less than 50% of the values missing. The arithmetic mean and geometric mean will be reported on at least 2 non-missing values; and the median, standard deviation and CV will be reported on at least 3 non-missing values. For $T_{max,}$ only N, median, minimum, and maximum will be calculated.

Individual (multiple-subject/spaghetti plots; and single-subject plots with Day 1/Day 8 overlaid) and mean MLN4924 plasma concentration-time data will be plotted against time after the start of the infusion by study Day for each DDI cohort. Linear and logarithmic scales will be used.

7.9.2 Pharmacodynamic Analysis (Part A)

Whole blood RT-PCR assay of genes (Part A)

Serial whole blood samples will be collected to measure pharmacodynamic effects via reverse-transcriptase polymerase chain reaction (RT-PCR) of NAE-regulated gene transcripts.

Eight genes of interest were identified as induced by NAE inhibition: ATF3, GCLM, GSR, MAG1, NQO1, SLC7A11, SRXN1, and TXNRD1. The percent change from baseline in the relative expression of each of the eight genes of interest will be calculated as $(2^{-(\text{Post Baseline Delta Ct} - \text{Baseline Delta Ct})}-1)*100$. The delta Ct is the mean Ct (over the replicates) for each gene of interest minus the mean Ct for the 4 housekeeping genes (18S, B2M, RPLP0, and UBC) calculated at each time point. A positive percent change is equivalent to an increase in expression after dosing with MLM4924.

Summary statistics of the percent change from baseline at each time point will be generated for each gene by DDI cohort. For each gene, the mean percent change from baseline over time will be plotted in a line plot with separate lines for each DDI cohort.

7.10 Other Outcomes

Not Applicable

7.11 Safety Analysis

Safety analyses will be conducted separately for Part A and Part B.

Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes or abnormalities in the patient's physical examination, vital signs, ECG, and clinical laboratory results.

These analyses for Part A will be performed **by DDI cohort** using the safety population for Part A. Safety analyses for Part B will be performed **by treatment arm and DDI cohort** using the safety population for Part B who continue from Part A into Part B with at least one dose administration of study drugs during Part B.

7.11.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent AE for Part A is defined as any AE that occurs after administration of the first dose of study treatment during Part A and up through 30 days after the last dose of study drug during Part A for patients who do not continue into Part B or up through Part B C1D1 (predose) for patients who continue into Part B. Any event that is considered drug-related, regardless of the start date of the event for patients who do not continue into part B, or any event that is present at Part A Baseline but worsens in severity postbaseline is considered a TEAE.

A treatment-emergent AE for Part B is defined as any AE that occurs after administration of the first dose of study treatment during Part B and up through 30 days after the last dose of study drug during Part B, or any event that is present at Part B Baseline (C1D1 predose) but worsens in severity postbaseline.

AEs will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT) for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort. Percentages will be calculated for the Part A total, arm totals for Part B and the Part B total. 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

- Treatment-emergent AEs resulting in study drug discontinuation
- SAEs
- Treatment-emergent drug-related SAEs

Treatment-emergent AEs will be tabulated by SOC, HLT, PT, and highest intensity. Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term. Most commonly reported (at least 10% of all patients) treatment-emergent AEs by preferred term will also be summarized by dosing windows (Day 1-3, Day 4-7, Day 8-10, Day 11+) for Part A, and by treatment cycles (Cycle 1, Cycle 2-3, Cycle 4+) for Part B. Additionally, tabulations of AE (by SOC, HLT, and PT) vs grade intensity will be made separately for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort. All adverse events will also be reported in by-patient listings separately for Part A, and Part B, which will include the variable AE onset window (i.e., "Part A" or "Part B").

During Part B, all adverse events for patients who have dose modification in the standard of care treatments will be included in a by-patient listing. This listing should additionally include reduced doses during AE occurrence and omitted doses during AE occurrence. Reduced doses during AE occurrence refer to any dose level, administered during the period of AE onset date to AE ending date, which is lower than the dose closest but prior to AE onset date. Omitted doses during AE occurrence refer to any scheduled dose which is omitted during the period of AE onset date to AE ending date.

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 for Part A 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 study drug in Part A, and on or before the month and year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.
  - treatment emergent for Part B 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 study drugs in Part B, and on or before the month and year of the date of the last dose of study drugs in Part B plus 30 days.
- If the start date has year, but day and month are missing, the event will be considered:
  - treatment emergent for Part A if the year of the start date of the event is on or after the year of the date of the first dose of MLN4924 in Part A, and on or before the year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.

  - treatment emergent for Part B 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 drugs in Part B, and on or before the year of the date of the last dose of study drugs in Part B plus 30 days.

- If the start date of an event is completely missing, the event will be considered:
  - treatment emergent for Part A for patients who do not continue into Part B.
  - treatment emergent for Part A for patients who continue into Part B if the ending date of the event is before the date of the first dose of study drugs in Part B.
  - treatment emergent for both Part A and Part B for patients who continue into Part B if the ending date does not reflect whether the AE ends prior to the first dose of study drug in Part B.

7.11.1.1 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA SOC, HLT, and PT, and separately for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort. Similar summary will be generated for treatment emergent drug-related SAEs.

By-patient listings of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status) separately for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort.

The drug-related SAEs will also be presented separately for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort in by-patient listings.

Listings of treatment emergent SAEs on the first dose of MLN4924 will be generated for Part A.

7.11.1.2 Deaths

By-subject listings of the deaths will be presented separately for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort. All deaths occurring on-study will be displayed (regardless of treatment-emergent AE status). Deaths with start dates that are completely or partially missing will be imputed to the date of last contact. An on-study death is defined as a death that occurs between the first dose of study drug in Part A and 30 days after the last dose of study drug.

7.11.1.3 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of study drug will be summarized by MedDRA SOC, HLT, and PT and separately for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort.

By-patient listing of AEs resulting in discontinuation of study drug will be presented separately for Part A and Part B. All AEs resulting in discontinuation of study drug occurring on-study will be displayed (regardless of treatment emergent AE status).

7.11.1.4 Myalgia Events

Listings of patients who experience treatment emergent myalgia events will be presented separately for Part A, and Part B. The corresponding preferred terms include myalgia, musculoskeletal pain, and musculoskeletal discomfort.

7.11.1.5 Acute Renal Failure Events

Listings of treatment-emergent acute renal failure events will be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Acute phosphate nephropathy
- Acute prerenal failure
- Anuria
- Azotaemia
- Continuous haemodiafiltration
- Dialysis
- Haemodialysis
- Neonatal anuria
- Nephropathy toxic
- Oliguria
- Peritoneal dialysis
- Prerenal failure
- Renal failure
- Renal failure acute
- Renal failure neonatal
- Renal impairment
- Renal impairment neonatal
- Albuminuria
- Blood creatinine abnormal
- Blood creatinine increased
- Blood urea abnormal
- Blood urea increased
- Blood urea nitrogen/creatinine ratio increased
- Creatinine renal clearance abnormal
- Creatinine renal clearance decreased
- Creatinine urine abnormal
- Creatinine urine decreased
- Crystal nephropathy
- Glomerular filtration rate abnormal
- Glomerular filtration rate decreased
- Hypercreatininaemia
- Nephritis
- Oedema due to renal disease
- Protein urine present
- Proteinuria
- Renal function test abnormal
- Renal transplant
- Renal tubular disorder
- Renal tubular necrosis
- Tubulointerstitial nephritis
- Urea renal clearance decreased
- Urine output decreased

7.11.1.6 Liver Function Test Elevations

Listing of treatment-emergent liver function test (LFT) elevations will be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Liver function test
- Liver function test abnormal
- Alanine aminotransferase
- Alanine aminotransferase abnormal
- Alanine aminotransferase increased
- Aspartate aminotransferase
- Aspartate aminotransferase increased
- Mitochondrial aspartate aminotransferase increased
- Aspartate aminotransferase abnormal
- Blood alkaline phosphatase
- Blood alkaline phosphatase abnormal
- Blood alkaline phosphatase increased
- Blood bilirubin
- Bilirubin urine
- Bilirubin conjugated
- Blood bilirubin abnormal
- Blood bilirubin increased
- Urine bilirubin increased
- Bilirubin conjugated increased
- Blood bilirubin unconjugated increased
- Gamma-glutamyltransferase
- Gamma-glutamyltransferase abnormal
- Gamma-glutamyltransferase increased

7.11.1.7 Tachycardia Events

Listings of treatment-emergent tachycardia events will be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Extrasystoles
- Heart rate increased
- Heart rate irregular
- Rebound tachycardia
- Sinus tachycardia
- Supraventricular extrasystoles
- Supraventricular tachyarrhythmia
- Tachyarrhythmia
- Tachycardia
- Tachycardia paroxysmal

7.11.1.8 Hypertension

Listings of treatment-emergent hypotension will be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Blood pressure ambulatory decreased
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure orthostatic abnormal
- Blood pressure orthostatic decreased
- Blood pressure systolic decreased
- Hypotension
- Orthostatic hypotension

7.11.1.9 Anemia

The highest intensity of treatment emergent anemia will be summarized by administration of red blood cells as a concomitant medication, separately for Part A and Part B.

Listings of treatment-emergent anemia will also be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Anaemia of chronic disease
- Anaemia of malignant disease
- Anaemia
- Red blood cell count decreased
- Haemoglobin decreased
- Mean cell haemoglobin decreased
- Haematocrit decreased

7.11.1.10 Neutropenia

Listings of treatment emergent neutropenia will also be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Agranulocytosis
- Band neutrophil count decreased
- Band neutrophil percentage decreased
- Febrile neutropenia
- Idiopathic neutropenia
- Leukopenia
- Neutropenia
- Neutropenic infection
- Neutropenic sepsis
- Neutrophil count abnormal
- Neutrophil count decreased
- Neutrophil percentage abnormal
- Neutrophil percentage decreased

7.11.1.11 Overall Summary

The number and percentage of patients who experience any of the following treatment-emergent adverse events will be summarized separately for Part A by DDI cohort, and for Part B by treatment arm and DDI cohort:

- Any adverse event
- Grade 3 or higher adverse event

- Drug-related adverse event
- Drug-related Grade 3 or higher adverse event
- Serious adverse event
- Drug related serious adverse event
- Adverse events resulting in study drug discontinuation
- On-study deaths

Percentages will be calculated for the Part A total, arm totals for Part B and the Part B total.

7.11.2 Clinical Laboratory Evaluations

For the purposes of summarization, 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 summarization, ignoring the non-numeric qualifier.

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

Shift tables of the change in NCI CTC from baseline to the post baseline worst CTC grade will be generated for relevant measurements, separately for Part A and Part B. Graphical displays will be used to show changes in laboratory measures over time, separately for Part A, and Part B:

1. Box graphs of individual tests over time by DDI cohort for Part A, and by treatment arm for Part B.
2. Spaghettis plot of selected lab tests over time by treatment arm and DDI cohort for Part B
3. Scatter plots of baseline versus worst postbaseline values by DDI cohort for Part A and by treatment arm for Part B. Separate plotting characters will be used for each subgroup. These will be generated for only selected labs (see table below).

Panel	Test	CTCAE Shift Table	MTD Box Plots	Spaghetti Plots	Scatter Plots
Chemistry	Albumin	X	X		
	Alanine aminotransferase (SGPT)	X	X	X	
	Aspartate aminotransferase (SGOT)	X	X	X	
	Alkaline Phosphatase	X	X	X	
	Carbon Dioxide	X	X		
	Direct Bilirubin	X	X	X	
	Total Bilirubin	X	X	X	
	Blood urea nitrogen		X		X

Panel	Test	CTCAE Shift Table	MTD Box Plots	Spaghetti Plots	Scatter Plots
	Blood urea nitrogen (mg/dL)/Creatinine (mg/dL)		X		X
	Calcium	X	X		
	Chloride	X	X		
	Creatinine	X	X	X	
	Creatinine clearance		X		X
	Glomerular filtration rate (estimated)		X		X
	Glucose	X	X		
	Gamma-glutamyl-transpeptidase	X	X	X	
	Lactate dehydrogenase	X	X		
	Magnesium	X	X		
	Phosphate	X	X	X	
	Potassium	X	X		
	Sodium	X	X		
	Urate	X	X		
Hematology	Platelets	X	X	X	
	Hematocrit		X		
	Hemoglobin	X	X	X	
	White Blood Cells	X	X	X	
	Lymphocyte Count	X	X		
	Neutrophils (ANC)	X	X	X	
	Monocytes		X		
	Eosinophils		X		
	Basophils		X		

For patients with neutrophil lab results reported as segmented neutrophils and neutrophil bands, ANC will be calculated by the Sponsor (or designee) as:

ANC=total leukocyte count × total percentage of neutrophils (segmented neutrophils + band neutrophils)

Example:

If total leukocyte count = 4.3 x 103; segmented neutrophils = 48%; band neutrophils = 2%
Then: 4300 × (0.48 + 0.02) = 4300 × 0.5 = ANC of 2150

Creatinine clearance and estimated glomerular filtration rate (GFR) will be derived by the Sponsor (or designee) using the Cockcroft-Gault and chronic kidney disease epidemiology collaboration (CKD-epi) formulas as follows:

Cockcroft-Gault equation:

For males:

$$\text{Creatinine Clearance} = \frac{\left((140 - \text{age[years]}) * \text{weight[kg]}\right)}{0.81 * (\text{serum creatinine } [\mu\text{mol/L}])}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85 * \left((140 - \text{age[years]}) * \text{weight[kg]}\right)}{0.81 * (\text{serum creatinine } [\mu\text{mol/L}])}$$

A cap value of 125 will be set to creatinine clearance values (calculated from Cockcroft-Gault equation) higher than 125.

CKD-epi equation:

For males:

$$GFR = 141 * \min(\text{serum creatinine}/0.9,\ 1)^{-0.411} * \max(\text{serum creatinine}/0.9,\ 1)^{-1.209} * 0.993^{\text{Age}} *$$
$$1.159[\text{if race} = \text{black}]$$

For females:

$$GFR = 141 * \min(\text{serum creatinine}/0.7,\ 1)^{-0.329} * \max(\text{serum creatinine}/0.7,\ 1)^{-1.209} * 0.993^{\text{Age}} *$$
$$1.018 * 1.159[\text{if race} = \text{black}]$$

For purposes of the scatterplots, the worst value will be the largest value observed after baseline for BUN and BUN/creatinine ratio. The worst value will be the smallest value observed after baseline for creatinine clearance and GFR.

All chemistry and hematology lab data will also be presented in by-patient listings separately for Part A and Part B.

In addition, by-patient listings of selected urinalysis parameters will be generated separately for Part A and Part B. The parameters to be displayed include the patient ID, visit and the results from protein, glucose, occult blood, leukocyte esterase, and erythrocytes, leukocytes, bacteria, casts, and crystals from microscopic evaluation.

7.11.3 Vital Signs

Graphical displays will be used to show vital sign parameters over time, separately for the Part A by DDI cohort, and for Part B by treatment arm:

- Individual patient line graphs of temperature, diastolic blood pressure (DBP), systolic blood pressure (SBP), and heart rate over time for each dose level in each subgroup. These will be summarized for measurements taken in the sitting position.
- Box plots over time for temperature, DBP, SBP, and heart rate during Cycle 1 will be generated for each subgroup. These will be summarized for measurements taken in the sitting position.

In addition, orthostatic hypotension will be defined as a decrease in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of at least 10 mm Hg after the patient changes from a supine position to a standing position. Orthostatic heart rate will be defined as increase in heart rate of at least 20 beats/min after the patient changes from a supine position to a standing position.

Tables will be generated to summarize the following at baseline and post-baseline, separately for Part A by DDI cohort, and for Part B by treatment arm:

- Percentage of patients who experienced orthostatic hypotension at baseline
- Percentage of patients who had orthostatic heart rate at baseline
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate at baseline
- Percentage of patients who experienced orthostatic hypotension postbaseline
- Percentage of patients who had orthostatic heart rate postbaseline
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate postbaseline

Moreover, the summary table should also include the following:

- Percentage of patients who had orthostatic hypotension postbaseline and did not have orthostatic hypotension at baseline
- Percentage of patients who had orthostatic heart rate postbaseline and did not have orthostatic heart rate at baseline
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate postbaseline and had neither orthostatic hypotension nor orthostatic heart rate at baseline
- Percentage of patients who had orthostatic hypotension at baseline and did not have orthostatic hypotension postbaseline
- Percentage of patients who had orthostatic heart rate at baseline and did not have orthostatic heart rate postbaseline
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate at baseline and had neither orthostatic hypotension nor orthostatic heart rate postbaseline

Additional listings of patients who had orthostatic hypotension or orthostatic heart rate postbaseline will be presented separately for Part A and Part B. The listings will include the baseline and postbaseline heart rate, SBP, and DBP in both the supine and standing positions. The listings will also include the patient's age and whether they were taking a beta blocking agent as a concomitant medication. Patients should be considered to be taking a beta blocking agent during Part A if they are taking any of the following at Day 1 of Part A, or considered to be one during Part B if taking any at Cycle 1 Day 1 of Part B:

Acebutolol, Atenolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carteolol, Carvedilol, Celiprolol, Esmolol, Labetalol, Levobunolol, Metipranolol, Metoprolol, Nadolol, Nebivolol, Oxprenolol, Penbutolol, Pindolol, Propranolol, Sotalol, Timolol

Vital signs data will also be presented in by-patient listings, separately for Part A and Part B.

7.11.4 Electrocardiograms

The number and percentage of patients experiencing abnormal ECG results will be summarized over each time point, separately for Part A by DDI cohort, and for Part B by treatment arm.

Corrected QT intervals (QTcF and QTcB) will be derived by the Sponsor (or designee) using the following formulas.

$$QTcF = \frac{QT_{uncorrected}}{\left(\frac{60}{\text{Ventricular Rate}}\right)^{1/3}} \qquad QTcB = \frac{QT_{uncorrected}}{\sqrt{\frac{60}{\text{Ventricular Rate}}}}$$

ECG findings will also be presented in by-patient listings separately for Part A, and Part B.

ECG Parameter	Abnormal values
QT, QTcF and QTcB	New absolute values >450, >480 and >500
	Changes from baseline >30 and >60
HR	Decrease from baseline >25% and to a HR < 50
	Increase from baseline >25% and to a HR > 100
PR	Increase from baseline >25% and to a value >200
QRS	Increase from baseline >25% and to a value >110

7.11.5 Disseminated Intravascular Coagulation (DIC) and PT/PTT

Data from the DIC panel at screening and prothrombin/partial thromboplastin times will be presented in separate by-patient listings, separately for Part A and Part B.

7.11.6 Echocardiograms

Echocardiogram results (e.g. LVEF) will be presented in by-patient listings separately for Part A and Part B.

7.12 Interim Analysis

As this is a phase 1 study there is no formal interim analysis. There will be an ongoing review of safety data with the medical monitor and study investigators, as well as within an internal Safety Working Group and the Independent Data Monitoring Committee (IDMC).

A preliminary PK analysis will be conducted after the first 4 to 8 patients have completed the Fluconazole Arm (MLN4924 + fluconazole) of Part A. After review of the emerging data from the Fluconazole Arm, patient assignment to the first cohort in the Itraconazole Arm (8 mg/m^2 MLN4924 + itraconazole) will be initiated. Dose modifications of MLN4924 in the Itraconazole Arm may be reconsidered based on the magnitude of the interaction with the moderate CYP3A inhibitor fluconazole and the ability to accurately estimate PK parameters for DDI evaluation.

Following completion of the first 3 patients in the Itraconazole Arm 8 mg/m^2 MLN4924 cohort, preliminary PK data will be reviewed to guide expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients. If these emerging preliminary PK data indicate that the magnitude of the interaction with the strong CYP3A inhibitor itraconazole reaches the anticipated approximately 10-fold change, and individual drug exposures do not exceed those seen at doses of MLN4924 $\geq$ 110 mg/m^2, then up to 3 additional patients to provide at least 4 to 6 PK-evaluable patients will be enrolled. If the magnitude of the interaction with the strong CYP3A inhibitor itraconazole is much greater than anticipated (greater than the predefined safety margin of 14-fold), with individual MLN4924 exposures exceeding those seen at doses of MLN4924 $\geq$ 110 mg/m^2, then no additional patients will be enrolled in the Itraconazole Arm of Part A.

As of the implementation of Protocol Amendment 1, following completion of Part A by 3 PK-evaluable patients in the Safety Lead-in 15-mg/m^2 MLN4924 Cohort, safety and PK data will be reviewed to inform expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients in the 20-mg/m^2 MLN4924 Cohort. If the preliminary PK data from the safety lead-in cohort indicate that the magnitude of the interaction between the proposed 20-mg/m^2 MLN4924 dose and the strong CYP3A inhibitor itraconazole would be greater than the predefined safety margin (5-fold, with individual MLN4924 exposures potentially exceeding those seen at doses of MLN4924 $\geq$ 110 mg/m^2), then no patients will be enrolled in the 20-mg/m^2 MLN4924 Cohort. Dosing with intermediate doses of MLN4924 and/or evaluation of the drug interaction with the moderate CYP3A inhibitor, fluconazole, may then be reconsidered if it is deemed necessary to further enhance our understanding of the effect of CYP3A inhibition on the PK of MLN4924.

7.13 Changes in the Statistical Analysis Plan

- CCI [redacted]
- PK-PD analysis to study relationships between MLN4924 plasma exposure and pharmacodynamic effects in blood as stated in the protocol will be not performed in the SAP and TLFs for this analysis will not be generated

Reference materials for this statistical plan include Clinical Study Protocol C15011 Amendment 2 (dated 12APRIL2017), and the accompanying data collection documents (Annotated Case Report Form [CRF], version 0.0 dated 21MAY2014).

8.0 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.
2. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.