Title: A Phase 1b, Open-Label, Dose Escalation, Multi-arm Study of MLN4924 Plus Docetaxel, Gemcitabine, or Combination of Carboplatin and Paclitaxel in Patients With Solid Tumors

NCT Number: NCT01862328

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STATISTICAL ANALYSIS PLAN

A Phase 1b, Open-Label, Dose-Escalation, Multi-arm Study of MLN4924 Plus Docetaxel, Gemcitabine, or Combination of Carboplatin and Paclitaxel, in Patients with Solid Tumors

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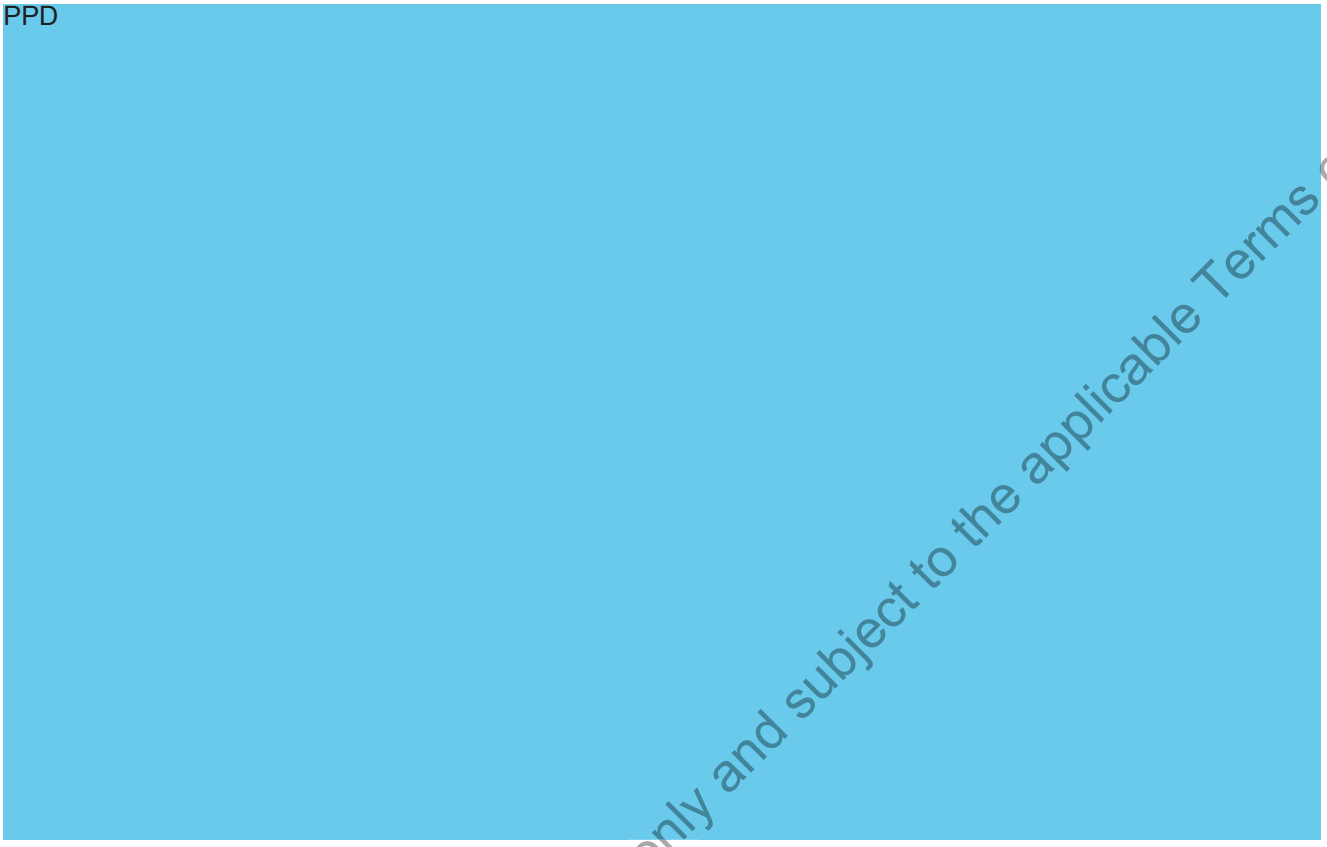
Approval Signatures

PPD



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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE(s)	adverse event (or events)
ALT	Alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the plasma concentration-time curve
AUMC	Area under the first moment curve
BSA	body surface area
CKD-epi	chronic kidney disease epidemiology collaboration
Cmax	Maximum plasma concentration
CR	complete response
CRM	continual reassessment method
CT	computed tomography
CV	coefficient of variation
DBP	diastolic blood pressure
DIC	disseminated intravascular coagulation
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study (visit)
CCI	
FE_K	Fractional Excretion of Potassium
FE_{NA}	Fractional Excretion of Sodium
FE_{PO4}	Fractional Excretion of Phophate
GFR	glomerular filtration rate
HLT	high level term
IDMC	Independent Data Monitoring Committee
IV	intravenous
KIM-1	kidney injury molecule-1
LFT	liver function test
LLQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF-κB	Nuclear (transcription) factor-kappa B
PD	progressive disease

PK	pharmacokinetic(s)
PMTD	predicted maximum tolerated dose
PR	partial response
PT	preferred term
PT/PTT	Prothrombin/partial thromboplastin times
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SAE	serious adverse event
SBP	systolic blood pressure
SD	stable disease
SOC	system organ class
t1/2	half-life
TAD	time after dosing
Vss	volume of distribution at steady state
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 address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This is an open-label, multicenter, phase 1b, dose-escalation study of MLN4924 in combination with docetaxel, paclitaxel and carboplatin, or gemcitabine in adult patients with solid tumors. The study includes a carboplatin lead-in phase where subjects receive MLN4924 + carboplatin only. The patient population will consist of patients 18 years of age or older with nonhematologic malignancies who, according to the investigator's medical judgment, could potentially benefit from treatment with any of the 3 standard of care therapies being studied.

It is expected that approximately 69 patients will be enrolled in this study. During the dose escalation portion of this study, the following dose levels of intravenous (IV) MLN4924 are planned to be studied in combination with docetaxel (Arm 1), paclitaxel + carboplatin (Arm 2), or gemcitabine (Arm 3).

MLN4924 + Docetaxel (Arm 1): A total of 4 dose levels of IV MLN4924 (15, 25, 37, and 50 mg/m^2) are planned to be studied in combination with 75 mg/m^2 of docetaxel. On Day 1 of each cycle when both drugs are administered, docetaxel will be administered first at a dose of 75 mg/m^2 IV over 1 hour. After a mandatory approximately15-minute time out (MLN4924-free period), MLN4924 will be administered IV. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days. No dose reduction of MLN4924 below 15 mg/m^2 is allowed.

MLN4924 + Carboplatin Lead-in Phase (before Arm 2): Before patients are enrolled in Arm 2 with paclitaxel + carboplatin, a cohort of approximately 3 to 6 patients will be treated with AUC6 dose of carboplatin in combination with MLN4924 at a dose of 15 mg/m^2. On Day 1 of each cycle, both compounds will be given. On Days 3 and 5, only MLN4924 will

be given. The duration of each cycle will be 21 days. If 1 dose limiting toxicity (DLT) is seen in this cohort, 3 additional patients will be treated with the same combination regimen. The carboplatin dose may be reduced to AUC5 for safety as needed. No dose reduction of MLN4924 below 15 mg/m^2 is allowed. No dose escalation of MLN4924 is planned in this cohort. The only chemotherapy agent that patients in this lead-in cohort will receive is carboplatin; these patients will not enroll on the MLN4924 + paclitaxel + carboplatin phase (Arm 2).

Observing no more than 1 DLT in this lead-in cohort will trigger enrollment in Arm 2 at AUC6 (MLN4924 [15 mg/m^2] + paclitaxel [200 mg/m^2] + carboplatin [AUC6]), and patients will be treated as described below for Arm 2.

If a total of 2 or more DLTs are observed in this cohort, enrollment on Arm 2 will open at reduced paclitaxel and carboplatin doses (MLN4924 [15 mg/m^2] + paclitaxel [175 mg/m^2] + carboplatin [AUC5]), and patients will be treated as described below for Arm 2.

MLN4924 + Paclitaxel + Carboplatin (Arm 2): During the dose escalation phase, a total of 4 dose levels of IV MLN4924 (15, 25, 37, and 50 mg/m^2) are planned to be studied in combination with paclitaxel and carboplatin. On Day 1 of each cycle when all 3 drugs are administered, paclitaxel is given first at a dose of 200 mg/m^2 (or 175 mg/m^2, if the dose was reduced in the carboplatin lead-in cohort) IV over 3 hours followed by carboplatin AUC6 (or AUC5 if the dose was reduced in the carboplatin lead-in cohort) over 30 minutes. After a mandatory approximately 15-minute time out (MLN4924-free period) 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.

MLN4924 + Gemcitabine (Arm 3): A total of 4 dose levels of IV MLN4924 (25, 50, 75, and 100 mg/m^2) are planned to be studied in combination with 1000 mg/m^2 of gemcitabine. Gemcitabine will be administered IV at a dose of 1000 mg/m^2 over 30 to 60 minutes, or as per current prescribing guidelines. After a 15-minute time out, MLN4924 will be administered. Patients will receive both agents on Days 1, 8, and 15, and the duration of each cycle will be 28 days.

After the determination of the maximum tolerated dose (MTD) of MLN4924 with docetaxel (Arm 1), paclitaxel + carboplatin (Arm 2), and gemcitabine (Arm 3), approximately 6 additional patients will be enrolled to each arm for a total of approximately 12 patients treated in each arm at the MTD to more fully characterize the safety, tolerability, and

pharmacokinetics (PK) of MLN4924 in combination with each standard of care regimen and to evaluate disease response.

An adaptive approach using a continual reassessment method (CRM) will be used for dose escalation (not including the Carboplatin lead-in). The CRM models the relationship between toxicities and dose level, which yields accurate and precise estimates of the MTD [1, 2, 3]. The dose toxicity relationship and the predicted MTD (PMTD) level will be updated as new data become available. The recommendation to escalate, de-escalate, or expand at the same dose level will be determined by comparing the PMTD level from the dose toxicity model to the prespecified dose levels. From the starting dose, subsequent increases in dose will be made according to the dose levels indicated for each arm; however, for safety reasons, no dose level will be skipped, and a minimum of 3 patients is required before escalating to the next dose level. Once at least 6 patients are treated at any dose level and the algorithm does not recommend escalation or de-escalation, this dose level may be considered the MTD.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [4]. DLTs are defined in Section 6.3.

Throughout the study, Eastern Cooperative Oncology Group (ECOG) performance status and adverse events (AEs) will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained and assessed to evaluate the safety and tolerability of MLN4924 in combination with docetaxel, paclitaxel + carboplatin, and gemcitabine (patients in the carboplatin lead-in cohort will receive MLN4924 + carboplatin only).

Blood samples (sparse sampling) for the determination of MLN4924 plasma concentrations and, if appropriate, its metabolites will be collected from each patient during Cycle 1 of treatment to contribute to a population PK analysis of MLN4924 co-administered with docetaxel, or paclitaxel + carboplatin, or gemcitabine.

Computed tomography (CT) scans with IV contrast of the chest, abdomen, and pelvis will be performed during screening. CT scans with IV contrast encompassing the known sites of disease will be performed at the end of Cycle 2 and then every other cycle thereafter, and at the End of Study (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 Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [5].

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1.2 Study Objectives

1.2.1 Primary Objectives

- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with docetaxel in patients with solid tumors
- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with paclitaxel and carboplatin in patients with solid tumors
- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with gemcitabine in patients with solid tumors

1.2.2 Secondary Objectives

- To evaluate disease response that may be observed with the combination of MLN4924 and docetaxel
- To evaluate disease response that may be observed with the combination of MLN4924, paclitaxel, and carboplatin
- To evaluate disease response that may be observed with the combination of MLN4924 and gemcitabine
- To measure plasma MLN4924 concentrations to contribute to a population PK analysis of MLN4924 co-administered with docetaxel, or paclitaxel + carboplatin, or gemcitabine in patients with solid tumors

1.2.3 Exploratory Objectives

CCI
[redacted]

2. POPULATIONS FOR ANALYSIS

2.1 Intent-to-Treat Population

Not applicable for a phase 1 study.

2.2 Per-Protocol Population

Not applicable for a phase 1 study.

2.3 Response-Evaluable Population

The response-evaluable population is defined as all patients who receive at least 1 dose of MLN4924, have measurable disease at baseline, and have at least 1 post baseline disease assessment. For the purposes of this study, all patients will be assumed to have measurable disease at baseline.

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

2.4 Safety Population

The safety population is defined as all patients who receive at least 1 dose of any study drug.

All safety analyses will be performed using the safety population.

2.5 Pharmacokinetics Population

Not applicable for this study.

2.6 Pharmacodynamics Population

Not applicable for this study.

2.7 DLT Evaluable Population

The DLT-Evaluable population is defined as all patients who either experience DLT during Cycle 1 or receive all scheduled doses of study drug on scheduled days during Cycle 1 without DLT. Patients in Arm 3 will still be considered DLT evaluable if they receive all doses of MLN4924 and receive gemcitabine on Days 1 and 8 only or on Days 1 and 15 only.

3. HYPOTHESES AND DECISION RULES

Not applicable for a phase I study.

4. INTERIM ANALYSIS

As this is a phase I 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 Monitor Committee (IDMC).

5. STATISTICAL METHODOLOGY

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

Due to the use of the CRM methodology for dose escalation, at a minimum, three patients will be dosed at any given dose level. Data may be pooled across dose levels for summary purposes. When appropriate, data will be summarized for the pooled dose levels below the MTD, at MTD, and for all patients. Data from each drug may be summarized separately. Patients will be analyzed at the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

5.1 Sample Size Justification

It is anticipated that approximately 69 patients will be enrolled combining the dose escalation for the determination of MTD for each combination, the cohort expansion at each MTD, and estimating approximately 6 patients enrolled in the carboplatin lead-in cohort.

Based on an estimated toxicity rate of 25% at 50 mg/m^2 in Arms 1 and 2 and at 100 mg/m^2 in Arm 3, computer simulations estimate that approximately 15 patients will be enrolled in each arm to determine the MTD of MLN4924 with standard of care.

Once each MTD is determined, approximately 6 additional patients (MTD expansion cohort) will be enrolled in each arm such that a total of approximately 12 patients will be enrolled and treated at each MTD to more fully characterize the safety, tolerability, and PK of MLN4924 with standard of care. These enrollment rules are based on the binomial probability assumption that if a particular toxicity occurs in 12.5% of the entire patient population, there is an 80% probability of observing at least 1 occurrence of that toxicity in 12 patients.

5.2 Randomization and Stratification

As this is a phase 1 study using a CRM algorithm to allocate patients to each dose level, there is no randomization in this study. Patients will be assigned to a treatment arm based on investigator judgment.

5.3 Unblinding

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

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing efficacy and safety data will be performed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. MLN4924 concentration values missing the corresponding sampling date and time records will be excluded from PK analysis.

5.4.2 Definition of Baseline Values

Unless otherwise specified, for each safety parameter, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. For the analysis of ECG data and urine safety data (e.g. Kidney Injury Molecule-1 (KIM-1)), the baseline value is the average of the screening and Cycle 1 Day 1 predose values, if both are

available. For KIM-1 only, the screening value will be within 3 days of the Cycle 1 Day 1 dose.

5.4.3 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 post dose.

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, Loss to Follow-up

Patients in the escalation phase who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced. Generally no additional patients will be enrolled due to withdrawals, dropouts, or loss to follow-up.

5.5 Patient Disposition

A tabulation of patient disposition data will include the number of patients for the following categories: patients treated (safety population), patients in the DLT-evaluable population, patients in the response-evaluable population, and patients discontinued from the study. The primary reason for study treatment discontinuation will also be summarized in this table.

All data will be summarized by each arm and MLN4924 dose level. Percentages will be based on the number of patients in the safety population, and they will be calculated for MTD, and the study total.

Data concerning patient disposition (eg reason for study termination, patient population) will be presented in by-patient listings.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Baseline demographics will be summarized separately for patients in the safety population by each arm and MLN4924 dose level. Baseline 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 by the Sponsor (or its designee) using the following formula based on the patient's height and weight at baseline:

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

No inferential statistics will be generated.

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

5.6.2 Inclusion/Exclusion Criteria

All inclusion/exclusion information on enrolled patients will be included in a by-patient listing. The listing 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 in the clinical trial management system will be reviewed, and significant protocol deviations will be identified and summarized 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.

5.6.3 Medical History

5.6.3.1 General Medical History

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).

5.6.3.2 Disease-Specific History

Not applicable for this study.

5.6.4 Baseline Disease Status

Baseline disease characteristics (disease type, disease stage, sites of involvement, time since initial diagnosis) will be summarized separately for patients in the safety population by each

arm and MLN4924 dose level. ECOG performance status will be summarized similarly in the same table. Separate by-patient listings will also be presented for baseline disease characteristics and ECOG performance status.

Information on prior therapies will be summarized separately for patients in the safety population by each arm and MLN4924 dose level (where applicable). For each arm and MLN4924 dose level (where applicable), summarized information on prior therapies will include:

- Number of patients with prior antieoplastic therapy
- Months from last dose of prior chemotherapy to first dose
- Number of patients with prior radiation
- Months from last prior radiation to first dose
- Number of patients with prior surgery or non-radiation procedures

In addition, prior chemotherapy regimens will be tabulated by MLN4924 dose level for each study arm. A second tabulation will summarize the following:

- Percentage of patients in Arm 1 (MLN4924+Docetaxel) receiving any taxane-containing regimen prior to dosing in MLN4924
- Percentage of patients in Arm 2 Lead-In (MLN4924+Carboplatin) receiving any platinum-containing regimen prior to dosing in MLN4924
- Percentage of patients in Arm 2 (MLN4924+ Paclitaxel+Carboplatin) receiving any regimen containing a taxane but not a platinum prior to dosing in MLN4924
- Percentage of patients in Arm 2 (MLN4924+ Paclitaxel+Carboplatin) receiving any regimen containing a platinum but not a taxane prior to dosing in MLN4924
- Percentage of patients in Arm 2 (MLN4924+ Paclitaxel+Carboplatin) receiving any regimen containing both a platinum and a taxane prior to dosing in MLN4924
- Percentage of patients in Arm 3 (MLN4924+Gemcitibine) receiving any gemcitibine-containing regimen prior to dosing in MLN4924

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 PACLITAXEL+TRASTUZUMAB
Platinum-containing regimens	BEVACIZUMAB+CARBOPLATIN+PACLITAXEL BEVACIZUMAB+CISPLATIN+DOCETAXEL BEVACIZUMAB+CISPLATIN+PACLITAXEL CAPECITABINE+CISPLATIN CAPECITABINE+CISPLATIN+EPIRUBICIN CAPECITABINE+EPIRUBICIN+OXALIPLATIN CAPECITABINE+OXALIPLATIN CARBOPLATIN (PARAPLATIN-AQ) CARBOPLATIN+ETOPOSIDE CARBOPLATIN+FLUOROURACIL CARBOPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL+TRASTUZUMAB CETUXIMAB+CISPLATIN+VINBLASTINE CETUXIMAB+CISPLATIN+VINORELBINE CISPLATIN (PLATINOL) CISPLATIN+DOCETAXEL CISPLATIN+DOCETAXEL+FLUOROURACIL

	CISPLATIN+EPIRUBICIN+FLUOROURACIL CISPLATIN+ETOPOSIDE CISPLATIN+FLUOROURACIL CISPLATIN+FLUOROURACIL+LEUCOVORIN CALCIUM CISPLATIN+GEMCITABINE CISPLATIN+IRINOTECAN CISPLATIN+PACLITAXEL CISPLATIN+PEMETREXED CISPLATIN+VINBLASTINE FLUOROURACIL+LEUCOVORIN CALCIUM+OXALIPLATIN FLUOROURACIL+OXALIPLATIN OXALIPLATIN (ELOXATIN)
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 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
Gemcitibine-containing regimen	CISPLATIN+GEMCITABINE GEMCITABINE (GEMZAR) GEMCITABINE+PACLITAXEL

5.7 Treatments and Medications

5.7.1 Concomitant Medications

All concomitant medications will be mapped to generic terms according to the World Health Organization (WHO) drug dictionary. The number and percentage of patients in the safety population taking concomitant medications will be tabulated by WHO drug generic term.

Tabulations will be performed for patients in the safety population by MLN4924 dose level in each arm. Concomitant procedures will not be coded.

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

5.7.2 Study Treatments

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 approximately15-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 the Arm 2 Lead-In Phase (MLN4924 + Carboplatin), patients will be treated with AUC6 dose of carboplatin in combination with MLN4924. On Day 1 of each cycle, both compounds will be given. 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 200 mg/m^2 (or 175 mg/m^2, if the dose was reduced in the carboplatin lead-in cohort) IV over 3 hours followed by carboplatin AUC6 (or AUC5 if the dose was reduced in the carboplatin lead-in cohort) 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.

For Arm 3 (MLN4924 + Gemcitabine), patients will be administered gemcitibine at a dose of 1000 mg/m^2 IV over 30-60 minutes. After a mandatory approximately15-minute time out, MLN4924 will be administered. Patients will receive both agents on Days 1, 8, and 15, and the duration of each cycle will be 28 days.

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

5.7.2.1 Extent of Exposure

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 dose level to which patients were initially assigned, as well as for all patients. Patients will be considered to have been treated for a cycle if they receive at

least one dose of MLN4924 during the 21 (or 28) days of that cycle. Percentages will be calculated by dose level and for all the patients.

The mean number of doses per cycle will be calculated for each patient and summarized for each dose level and total for the arm.

For MLN4924, Percent Dosing Intensity will be calculated using the following equations for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg):

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

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

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

Daily Expected Dose and Daily Prepared Dose may differ if there are dose decreases. 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 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 Dosing Intensity for MLN4924 will be based on the following formulas:

$$\text{Total Dose Received} = \text{Sum of Daily Dose Received across all days that MLN4924 was administered}$$

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

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

Total dose expected will be calculated based on the BSA measured at baseline. 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 dose level, as well as for all patients.

For each of the standard of care drugs, the extent of exposure will be summarized in a similar manner as MLN4924. A separate column will be generated for each dose level of MLN4924, and the number of cycles of standard of care drug administered will be summarized.

The mean number of doses per cycle will be calculated for each patient and summarized by dose levels and the study total.

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:

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

$$\text{Daily Expected Dose (Carboplatin)} = \text{Dose Level Assigned at Study Entry (AUC)} * (\text{Glomerular filtration rate} + 25)$$

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

$$\text{Daily Prepared Dose (Carboplatin)} = \text{Scheduled Dose Level (AUC)} * (\text{Glomerular filtration rate} + 25)$$

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

Dosing intensity for each standard of care drug will be summarized by MLN4924 dose level in a similar manner to MLN4924 dosing intensity.

5.7.2.2 Treatment Compliance and Modifications

The actions on study drugs (Dose Held, Dose Reduced, Dose Interrupted, Dose Delayed, Dose Incomplete, or Discontinued) will be summarized by MLN4924 dose level for MLN4924 and each standard of care drug. Data will be summarized for Cycle 1 only as well as all cycles combined. A patient will count only once for each type of action.

5.8 Efficacy Analyses

Since this is a phase I study, 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], and progressive disease [PD]) will be presented for each dose level. Percentages will be calculated for all patients, and those at the MTD. All evaluations of response will be conducted using the response-evaluable population.

For each patient in the expansion cohorts, 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 across MTD expansion patients in each arm. Unscheduled visits will also be included in such displays.

The duration of disease response (CR or PR) and the duration of CR will be presented in a by-patient listing for all response-evaluable patients with CR or PR. Duration of response (or duration of CR) are the time, in both days and months, from the date of first documented response (or CR) per the investigator response assessment to the date of first documentation of PD after the first documented response (or CR), or the date of last disease assessment if the patient discontinues treatment before PD. In addition, the date of first response, the date of first CR, the date of first documentation of PD after the first response, the number of cycles of response, and the number of cycles of CR will be shown. The duration of response (in months), the duration of CR (in months), the number of cycles of response, and the number of cycles of CR will also be summarized descriptively at each dose level of MLN4924 for all response-evaluable patients. The same table will also summarize the time to first response and time to first CR. Separate summaries will be generated for each arm of the study.

The duration of SD or better will be presented in a by-patient listing for all response-evaluable patients. Duration of SD or better is the time from the date of first dose to the date of first documentation of PD, 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 at each dose level of MLN4924 for all response-evaluable patients. Separate summaries will be generated for each arm of the study.

A separate listing will be generated for patients who are on treatment for at least 5 cycles. 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.

5.8.1 Primary Efficacy Endpoint

Not applicable for this study.

5.8.2 Secondary Efficacy Endpoints

Not applicable for this study.

5.8.3 Other Efficacy Endpoints

Not applicable for this study.

5.9 Pharmacokinetic and Biomarker Analysis

5.9.1 Pharmacokinetic Analyses

Blood samples (~ 3 mL each) will be collected at the following time points:

Patients in Dose Escalation (Arms 1 and 2)

- Day 1:
  - Within 1 hour before the start of MLN4924 infusion
  - At the end of the MLN4924 infusion (immediately before switching off the infusion pump)
  - At 1.5 hours (± 15 minutes) and 3 hours (± 30 minutes) after completion of the MLN4924 infusion
- Day 2:
  - 20 hours (± 2 hours) after end of MLN4924 Cycle 1, Day 1 infusion
- Day 3: Within 10 minutes before the start of the MLN4924 infusion

Patients in Dose Escalation (Arm 3)

- Day 1:
  - Within 1 hour before the start of MLN4924 infusion
  - At the end of the MLN4924 infusion (immediately before switching off the infusion pump)
  - At 1.5 hours (± 15 minutes) and 3 hours (± 30 minutes) after completion of the MLN4924 infusion
- Day 2:

- 20 hours (± 2 hours) after end of MLN4924 Cycle 1, Day 1 infusion

Patients in MTD Expansion (Arm 1)

- Day 1:
  - Within 1 hour before the start of MLN4924 infusion
  - At the end of the MLN4924 infusion (immediately before switching off the infusion pump)
  - At 1.5 hours (± 15 minutes), 3 hours (± 30 minutes), and 7 hours (± 45 minutes) after completion of the MLN4924 infusion
- Day 2:
  - 20 hours (± 2 hours) after end of MLN4924 Cycle 1, Day 1 infusion
- Day 3: Within 10 minutes before the start of the MLN4924 infusion
- Day 5:
  - Within 10 minutes before the start of MLN4924 infusion
  - At the end of the MLN4924 infusion (immediately before switching off the infusion pump)
  - At 1.5 hours (± 15 minutes), 3 hours (± 30 minutes), and 7 hours (± 45 minutes) after completion of the MLN4924 infusion
- Day 6:
  - 20 hours (± 2 hours) after end of MLN4924 Cycle 1, Day 5 infusion

Patients in MTD Expansion (Arm 2)

- Day 1:
  - Within 1 hour before the start of MLN4924 infusion
  - At the end of the MLN4924 infusion (immediately before switching off the infusion pump)
  - At 1.5 hours (± 15 minutes), 3 hours (± 30 minutes), and 6 hours (± 45 minutes) after completion of the MLN4924 infusion
- Day 2:
  - 20 hours (± 2 hours) after end of MLN4924 Cycle 1, Day 1 infusion
- Day 3: Within 10 minutes before the start of the MLN4924 infusion
- Day 5:
  - Within 10 minutes before the start of MLN4924 infusion

  - At the end of the MLN4924 infusion (immediately before switching off the infusion pump)
  - At 1.5 hours (± 15 minutes), 3 hours (± 30 minutes), and 6 hours (± 45 minutes) after completion of the MLN4924 infusion

- Day 6:
  - 20 hours (± 2 hours) after end of MLN4924 Cycle 1, Day 5 infusion

Patients in MTD Expansion (Arm 3)

- Day 1:
  - Within 1 hour before the start of MLN4924 infusion
  - At the end of the MLN4924 infusion (immediately before switching off the infusion pump)
  - At 1.5 hours (± 15 minutes), 3 hours (± 30 minutes), and 7 hours (± 45 minutes) after completion of the MLN4924 infusion
- Day 2:
  - 20 hours (± 2 hours) after end of MLN4924 Cycle 1, Day 1 infusion

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.

All individual MLN4924 concentration-time data will be pooled to describe the population PK of MLN4924. As data permit, a nonlinear regression mixed effects model (NONMEM software) will be used to assess MLN4924 exposure when administered in combination with docetaxel, or carboplatin/paclitaxel, or gemcitabine. Individual metabolite data may also be assessed, as deemed appropriate. If appropriate, historical data may be used in this analysis to increase the robustness of the model and precision of estimated PK parameters and compare with single agent data. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses will be reported separately.

Plasma concentration values below the lower limit of quantification (<LLQ) of the bioanalytical assay will be set to zero for analysis. Actual PK sampling collection dates/times will be used in the analysis. 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.

As data permit, individual and mean MLN4924 plasma concentration-time data will be tabulated and plotted for each combination therapy.

5.9.2 Biomarker Analysis

5.9.2.1 Candidate Tumor Biomarkers and Tumor Biomarkers of Response

Any biomarker related analysis including ERCC1 in Arm 2 of MLN4924 in combination with Paclitaxel and Carbophatin, PSMB1, NGS will be included in a separate biomarker analysis plan if appropriate.

5.10 Safety Analyses

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.

The following analyses will be performed using the safety population.

5.10.1 Adverse Events

5.10.1.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline.

AEs will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT). Summary tabulations include the following subsets:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Grade 4 or higher treatment-emergent AEs

- Grade 4 or higher drug-related treatment-emergent AEs
- Grade 3 drug-related treatment-emergent AEs
- Grade 4 drug-related treatment-emergent AEs
- Treatment-emergent AEs resulting in study drug discontinuation
- SAEs
- 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 treatment cycle of onset (Cycle 1, Cycle 2-3, Cycle 4-5, Cycle 6+). Additionally, for patients dosed at MTD, a tabulation of AE (by SOC, HLT, and PT) vs grade intensity will be made. Separate summaries will be generated for each arm. All adverse events will also be reported in by-patient listings.

All adverse events for patients who have dose modification in standard of cares will also be included in a by-patient listing. This listing should additionally include reduced doses during AE occurrence and omitted doses durign 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 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 MLN4924 and on or before the month and year of the date of the last dose of MLN4924 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 MLN4924 and on or before the year of the date of the last dose of MLN4924 plus 30 days.

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

5.10.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA SOC, HLT, and PT.

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

The drug-related SAEs will also be presented in a by-patient listing.

An additional listing of treatment emergent C1D1 grade 2 or higher SAEs will also be generated.

5.10.1.3 Deaths

A by-subject 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 after the last dose of study drug.

5.10.1.4 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.

A by-patient 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 (DLTs)

A by-patient listing of DLTs in Cycle 1 will be presented by dose level for patients in the DLT-evaluable population. Patients will be grouped by the arm and MLN4924 dose level to

which they were originally assigned at enrollment, including those who receive subsequent treatment at a lower dose level due to intra-patient dose modification.

5.10.1.6 Myalgia Events

A listing of patients who experience treatment emergent myalgia events will be presented.

5.10.1.7 Acute Renal Failure Events

A listing of treatment-emergent acute renal failure events will be generated. 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

5.10.1.8 Liver Function Test (LFT) Elevations

A listing of treatment-emergent LFT elevations will be generated. 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

5.10.1.9 Tachycardia Events

A listing of treatment-emergent tachycardia events will be generated. 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

5.10.1.10 Hypotension

A listing of treatment-emergent hypotension will be generated. 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

5.10.1.11 **Anemia**

A separate table will display a cross-tabulation of patients who report a PT of anemia and those who receive a concomitant medication of red blood cells at any point during the study.

A listing of treatment-emergent anemia will also be generated. 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

5.10.1.12 **Neutropenia**

A listing of treatment-emergent neutropenia will also be generated. 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

5.10.1.13 **Overall Summary**

The number of patients who experience any of the following groups will be summarized by dose level:

- Any adverse event (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5))
- Drug-related adverse event (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5))
- Serious adverse event

- Drug related serious adverse event
- Adverse events resulting in study drug discontinuation
- On-study deaths

Percentages will be calculated for each dose and all the patients.

5.10.2 Laboratory Data

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. Graphical displays will be used to show changes in laboratory measures over time for patients:

1) Box graphs of individual tests over time for patients at MTD.
2) Scatter plots of baseline versus worst post-baseline values for all patients. Separate plotting characters will be used for each dose. These will be generated for only selected labs (see table below).

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

Panel	Test	CTCAE Shift Table	MTD Box Plots	Scatter Plots
	Chloride	X	X	
	Creatinine	X	X	
	Creatinine clearance		X	X
	Glomerular filtration rate (estimated)		X	X
	Glucose	X	X	
	Gamma-glutamyl-transpeptidase	X	X	
	Lactate dehydrogenase	X	X	
	Magnesium	X	X	
	Phosphate	X	X	
	Potassium	X	X	
	Sodium	X	X	
	Urate	X	X	
Hematology	Platelets	X	X	
	Hematocrit		X	X
	Hemoglobin	X	X	
	White Blood Cells	X	X	
	Lymphocyte Count	X	X	
	Neutrophils (ANC)	X	X	
	Monocytes		X	X
	Eosinophils		X	X
	Basophils		X	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 10^3; 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:

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

For females:

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

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:

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

All chemistry and hematology lab data will also be presented in by-patient listings.

In addition, a listing of selected urinalysis parameters will be presented to display the patient ID, visit and the results from protein, glucose, occult blood, erythrocytes (from microscopic evaluation), leukocyte esterase, and leukocytes (from microscopic evaluation). Patients will be grouped by arm and MLN4924 dose level. All urinalysis parameters will be presented in by-patient listings.

5.10.3 **Electrocardiograms**

The number and percent of patients experiencing abnormal ECG results will be summarized for each time point on Days 1 by MLN4924 dosing levels.

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.

5.10.4 Vital Signs

Graphical displays will be used to show vital sign parameters over time:

- 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 arm. These will be summarized for measurements taken in the sitting position.

- Boxplots over time for temperature, DBP, SBP, and heart rate during Cycle 1 will be generated at the MTD for each arm. These will be summarized for measurements taken in the sitting position.

- Boxplots of change from baseline over time for temperature, DBP, SBP, and heart rate during Cycle 1 will be generated at the MTD for each arm. 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.

A table will be generated to summarize the following at baseline and post dose for each SOC and MLN4924 dose level:

- 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 post dose
- Percentage of patients who had orthostatic heart rate post dose

- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate post dose

Moreover, the summary table should also include the following:

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

An additional listing of patients who had orthostatic hypotension or orthostatic heart rate post dose will be presented. The listing will include the baseline and post dose heart rate, SBP, and DBP in both the supine and standing positions. The listing 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 if they are taking any of the following at C1D1:

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

All vital sign data will also be presented in a by-patient listing.

5.10.5 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.

5.10.6 Echocardiograms

Echocardiogram results (e.g. left ventricular ejection fraction) will be presented in by-patient listing. The listing will also specify whether the values were captured via MUGA.

5.10.7 Urine Safety Assessment

Multi-panel line plots will be generated for each dose level and arm. Separate plots will be generated for Cycle 1 data and Cycle 2+ data. The following measures will be summarized::

- Urine KIM-1/urine creatinine ratio (calculated value and percent change from baseline):

$$\frac{\text{urine KIM-1 (ng/mL)}}{0.01(\text{dL/mL}) * \text{urine creatinine (mg/dL)}}$$

- Urine albumin/urine creatinine ratio:

$$\frac{\text{urine albumin } (\mu\text{g/mL})}{0.01(\text{dL/mL}) * \text{urine creatinine (mg/dL)}}$$

- Fractional Excretion of Phosphate (FE_{PO4}):

$$\frac{[\text{urine phosphate(mg/dL)}] * [\text{serum creatinine } (\mu\text{mol/L})]/88.4}{[\text{urine creatinine (mg/dL)}] * [\text{serum phosphate(mmol/L)}]/0.3229} * 100$$

- Fractional Excretion of Sodium (FE_{NA}):

$$\frac{[\text{urine sodium(mmol/L)}][\text{serum creatinine } (\mu\text{mol/L})]/88.4}{[\text{urine creatinine (mg/dL)}][\text{serum sodium(mmol/L)}]} * 100$$

- Fractional Excretion of Potassium (FE_K)

$$\frac{[\text{urine potassium(mmol/L)}][\text{serum creatinine } (\mu\text{mol/L})]/88.4}{[\text{urine creatinine (mg/dL)}][\text{serum potassium(mmol/L)}]} * 100$$

Individual patients are represented by separate lines. A line representing the average for all patients in a given arm and dose level will also be included.

For the plots of the ratio of Urine Albumin/ Urine Creatinine, two horizontal lines will be drawn at 30 mg/g and 300 mg/g, where the horizontal line of 30 mg/g will be labeled with "microalbuminuria: 30-300 mg/g", and the line of 300 mg/g with "macroalbuminuria: > 300 mg/g". In addition, an additional set of plots for the ratio of Urine Albumin/ Urine Creatinine will be generated for patients whose baseline ratios of Urine Albumin/ Urine Creatinine are less than 50 mg/g.

Results of urine safety assessments will also be presented in by-patient listings.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Reference materials for this statistical plan include Clinical Study Protocol C15010 (dated 08MAR2013), Administrative Change Letter #1 (dated 12 June 2013), and the accompanying data collection documents (Annotated Case Report Form [CRF], version 2.0 dated 09JUL2013).

The following changes have been made to the planned analyses from the protocol:

- Sections 5.10.2, 5.10.4 and 5.10.5: Due to the small number of patients in each dose level summary statistics for laboratory data, ECG, vital signs may not be presented.
- The definitions of the DLT-evaluable population was updated for clarity
- The definition of the PK-evaluable population was removed as there will be no PK analysis to estimate PK parameters.

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

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

7.2 Rules and Definitions

Patient populations are defined in Section 2.

Baseline values are defined as in Section 5.4.2.

Treatment emergent AEs are defined as in Section 5.10.1.1.

8. REFERENCES

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