Title: Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies

NCT Number: NCT01899053

SAP Approve Date: 18 Aug 2016

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

STUDY NUMBER: C32001

A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies

PHASE 1

Version**: FINAL**

Date**:** 18 Aug 2016

Prepared by:

Protected Personal Data

Based on:

Protocol Version: Amendment 4

Protocol Date: 02 April 2014

1.1 Approval Signatures

Study Title: A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies

Approvals:

Protected Personal Data

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

4EBP1	4E-binding protein
AE	adverse event
AKT	protein kinase B (PKB)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{24h}	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the end of the dosing interval
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	single-dose maximum (peak) concentration
CR	complete response
CRF	case report form
DDI	drug-drug interaction
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
EOS	End of Study (visit)
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MTuW	Monday, Tuesday, Wednesday (dosing schedule)
MWF	Monday, Wednesday, Friday (dosing schedule)
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate

PD	pharmacodynamics
PI3K	phosphoinositol-3-kinase
PK	pharmacokinetics
PR	partial response

QD	*quaque die*; each day; once daily
QT	QT interval (millisec) of electrocardiograph
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
S6	ribosomal protein S6 kinase
$t_{1/2}$	terminal disposition half-life
ULN	upper limit of normal
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

- To evaluate the safety profile and to determine DLTs, MTDs and/or RP2Ds, and dosing schedules of oral MLN0128 + MLN1117 in patients with advanced nonhematologic malignancies

- To characterize the single- and multiple-dose plasma PK of MLN0128 + MLN1117 in patients with advanced nonhematologic malignancies

4.2 Secondary Objectives

- To evaluate evidence of antitumor activity of MLN0128 + MLN1117

4.3 Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]

4.4 Study Design

This study is a multicenter, open-label, phase 1b trial of MLN0128 (an oral mTORC1/2 inhibitor) in combination with MLN1117 (an oral inhibitor of the PI3Kα isoform) when administered to adult patients with advanced nonhematological malignancies for whom standard, curative, or life-prolonging anticancer treatment does not exist or is no longer effective. The study will consist of 2 stages: a (dose) Escalation Stage followed by an Expansion Stage. In the Escalation Stage, 2 dosing regimens for the combination will be evaluated in separate treatment

arms. The phrase "study drug" or "MLN0128 + MLN1117" refers to combination dosing of MLN0128 + MLN1117.

In the Escalation Stage, patients will be enrolled into dose escalation cohorts at different combination doses and schedules of MLN0128 and MLN1117 using a standard 3 + 3 approach to determine the maximum tolerated doses (MTDs) and/or recommended phase 2 doses (RP2Ds) in each treatment arm and optimal dosing schedules to be implemented in the Expansion Stage. Study drug will be administered in 28-day cycles. In Treatment Arm A, MLN0128 will be administered once daily every day (QD) and MLN1117 will be administered once daily on Monday, Wednesday, and Friday (MWF) of each week. In Treatment Arm B and Arm C, both MLN0128 and MLN1117 will be administered QD on Monday, Tuesday, and Wednesday (MTuW) of each week.

Patients will be enrolled in the Expansion Stage to further characterize the safety, tolerability, PK, and pharmacodynamics of MLN0128 in combination with MLN1117. This stage will consist of a Mutual DDI PK Expansion Cohort and tumor-specific cohorts. The combination dose and schedule from 1 of the treatment arms evaluated in the Escalation Stage will be implemented in the Mutual DDI PK Expansion Cohort. The combination of doses and schedules from any of the treatment arms evaluated in the Escalation Stage may be implemented in each individual tumor-specific expansion cohort. The tumor types selected for evaluation in the Expansion Stage will be based on safety and antitumor activity observed during Study C32001, by the emerging results of other MLN0128 and/or MLN1117 clinical studies, and by emerging data from nonclinical experiments. Likewise, the schedules for combination dosing in an individual tumor-specific cohort of the Expansion Stage will be based on clinical observations made during the Escalation Stage. The dose, schedule, and selection of tumor types for the tumor-specific cohorts will be identified in a protocol amendment.

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. AEs will be assessed, and laboratory values, vital signs, physical exam findings, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of MLN0128 + MLN1117.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- AEs, SAEs, assessments of clinical laboratory values, physical exam findings, electrocardiograms (ECGs), and vital sign measurements

- MLN0128 and MLN1117 plasma PK parameters including, but not limited to, C_{max}, T_{max}, area under the concentration-time curve from time 0 to the end of the dosing interval (AUC_{last}), $t_{1/2}$, apparent oral clearance (CL/F), peak-to-trough ratio, and accumulation ratio

5.2 Secondary Endpoints

- Measures of disease response including objective response rate and duration of response, based on investigator's assessment and using if feasible, the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)

5.3 Exploratory Endpoints

- Company Confidential Information [redacted]

6.0 DETERMINATION OF SAMPLE SIZE

To estimate the number of patients for this study, it is assumed that 15% of enrolled patients will be non-evaluable. Approximately 152 patients will be enrolled into this study.

Of the 152 patient estimated to be enrolled, approximately 72 will be enrolled into the Escalation Stage. These patients will be divided into treatment arms which differ in combination dosing schedules to determine the MTDs and/or RP2Ds of MLN0128 + MLN1117 in each treatment arm. The number of patients enrolled in the Escalation Stage was determined by estimating the number of dose combinations to be evaluated and the number of potential evaluable patients not experiencing a DLT. It is estimated that 3 to 6 patients will be evaluated at each dose level per treatment arm.

After the final doses and schedules have been selected, approximately 80 patients will be enrolled in the Expansion Stage. This stage will consist of a Mutual DDI PK Expansion Cohort and tumor-specific cohorts.

In the Mutual DDI PK Expansion Cohort of the Expansion Stage, data from approximately 16 of the 20 treated patients must satisfy specific criteria to be included in statistical analysis of the effect of MLN0128 co-administration on MLN1117 PK and the effect of MLN1117 co-administration on MLN0128 PK. If fewer than 16 patients meet these criteria, additional patients will be enrolled in the Mutual DDI PK Expansion Cohort to reach a minimum sample size of 16 patients.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, unless specified otherwise.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data.

Unless otherwise specified, summary tabulations will be presented for each MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort.

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. Cycle 1 day 1 values are considered pre-dose. Screening values are considered baseline values if a cycle 1 day value is unavailable.

All statistical analyses will be conducted using SAS® Version 9.4.

7.1.1 Conventions for Missing Adverse Event Dates

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

- If the start date has a month and year but the day is missing, the event will be considered treatment emergent if the month and year of the start date of the event are:
    - On or after the month and year of the date of the first dose of study drug

      and
    - On or before the month and year of the date of the last dose of study drug plus 30 days
- If the start date has a year, but the day and month are missing, the event will be considered treatment emergent if the year of the start date of the event is:

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

  and

- On or before the year of the date of the last dose of study drug plus 30 days

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

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

7.2 Analysis Sets

The Safety Population consists of all enrolled patients who have received at least 1 dose of any study drug. All safety analyses will be based on the safety population.

The Pharmacokinetic DDI-evaluable population consists of all patients from the Mutual DDI PK Expansion Cohort with sufficient dosing and concentration-time PK data to reliably estimate PK parameters for statistical analyses of the effect of MLN0128 on MLN1117 PK and the effect of MLN1117 on MLN0128 PK. The PK DDI analyses will be performed using the PK DDI-evaluable population.

The pharmacodynamics population consists of patients with at least one pre and post baseline skin biopsy. The PD analyses will be performed using the pharmacodynamics population.

The Response-Evaluable Population consists of all patients who receive at least 1 dose of study drug, and have at least 1 post baseline disease assessment will be used for analyses of response. Response analyses will be performed using the response-evaluable population.

The DLT-evaluable population is defined as all patients who experience a DLT during Cycle 1, or receive all scheduled doses and complete all study procedures in Cycle 1 without experiencing a DLT.

7.3 Disposition of Subjects

The number and percentage of patients in each population will be presented by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort.

The number and percentage of patients who have discontinued study drug, the primary reason for discontinuing study drug, and still ongoing at the time of the data cutoff for the clinical study report will be summarized similarly. All percentages will be based on the number of patients in the safety population.

7.4 Demographic and Other Baseline Characteristics

Baseline demographic data (gender, age, race, ethnicity, weight, height, and body mass index) will be summarized for each of the treatment arms in the dose escalation stage, for the dose escalation stage total, and for the mutual DDI PK expansion cohort. Age will be calculated from the date of informed consent.

7.5 Medical History and Concurrent Medical Conditions

Baseline disease type (primary diagnosis), time since initial diagnosis (months), disease stage at study entry, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized for each of the treatment arms in the dose escalation stage, for the dose escalation stage total, and for the mutual DDI PK expansion cohort. The time since initial diagnosis in months is calculated as: (first dose date - date of initial diagnosis +1) /30.4375.

7.6 Medication History and Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term for the safety population by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort.

7.7 Study Drug Exposure and Compliance

The exposure to MLN0128/MLN1117 will be characterized by the cumulative dose (mg), planned dose (mg) and relative dose intensity (%) for each study drug. In addition, the number of treated cycles, number and percent of patients who had ≥1, ≥2, …, and ≥6 treated cycles, and the duration of treatment in weeks will be summarized.

A treated cycle is defined as a cycle in which the patient received any amount of study drug (MLN0128 or MLN1117).

Relative dose intensity (%) is defined as 100 * (cumulative dose received in mg) / (planned dose in mg). Planned dose is assigned dose level at study start * planned doses per cycle * maximum number of cycles.

Action on each study drug (MLN0128 and MLN1117) will be summarized for each cycle (Cycles 1 to 6), for patients who go beyond 6 cycles, and for all patients.

The extent of exposure and action on each study drug will be summarized by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort based on the safety population.

7.8 Efficacy Analysis

Efficacy is not the primary endpoint of the study. The secondary efficacy endpoints are overall response rate (ORR) and duration of response (DOR) based on investigator's assessment and using if feasible, the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).

The best overall response for each patient will be derived programmatically from among the reported responses based on the investigator assessment. The ORR is the percent of patients in the response evaluable population with a best response of CR or PR.

Summaries of the number and percentage of patients falling into each response category (eg, CR, PR, Stable Disease (SD), Progressive Disease), with ORR (CR + PR), and with CR + PR of any duration or SD > 6 months will be summarized by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort based on the response evaluable population.

The duration of SD will calculated for the patients with a best response of SD. Duration of SD is defined as the number of days from cycle 1 day 1 until progressive disease or until the last response assessment if there is no progressive disease.

The duration of response (DOR) will be calculated for patients with a best response of CR or PR. The DOR is defined as the time from the date of first documented response of CR/PR to the first

documented PD, or censored at the last response assessment date that is SD or better for a patient that has not progressed.

The investigator assessment of response (eg, CR, PR, stable disease [SD]) and whether symptomatic deterioration occurred at each visit will be provided in a data listing. In addition, the duration of SD, DOR, and the best overall response will be included in a data listing.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

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

7.9.1.1 Pharmacokinetic Concentrations

Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, median, minimum, and maximum) will be used to summarize the plasma concentrations of MLN0128 and MLN1117 on Cycle 1 Day 1 and Cycle 1 Day 24 for each MLN0128/MLN117 dose level within each arm in the dose escalation cohort, and on cycle 1 day 3, day 10, and day 17 for the mutual DDI PK expansion cohort.

BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing.

Linear and semi-logarithmic plots of the mean plasma concentration versus scheduled sampling time will be provided on Cycle 1 Day 1 and Cycle 1 Day 24 for each MLN0128/MLN117 dose level within each arm in the dose escalation cohort and on cycle 1 day 3, day 10, and day 17 for the mutual DDI PK expansion cohort (overlay onto one plot).

Linear and semi-logarithmic plots of individual plasma concentration versus actual sampling time will be provided (overlay Cycle 1 Day 1 and Cycle 1 Day 24 profiles for each individual for the dose escalation cohort, and Cycle 1 Days 3, 10, and 17 for the mutual DDI PK expansion cohort). All individual patient plasma concentration data will be in a data listing.

7.9.1.2 Pharmacokinetic Parameters

PK parameters will be estimated using non-compartmental methods with [redacted] Professional Version 6.1 or higher ([redacted]). The plasma PK

parameters will be estimated from the concentration-time profiles for all PK population patients. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of deviation, geometric mean, median, minimum value, and maximum value) will be used to summarize the calculated PK parameters. For T_{max}, only median, minimum value, and maximum value will be presented. All individual patient PK parameter data will be in a data listing.

Data permitting, the following PK parameters will be calculated for MLN0128 and MLN1117:

- Area under the plasma concentration-time curve from time 0 to time of last measurable concentration (AUC0-last)
- Area under the plasma concentration-time curve from time 0 to infinity (AUC0-inf)
- Area under the plasma concentration-time curve from time 0 to 24 hr (AUC24hr)
- Observed maximum plasma concentration (Cmax)
- Time to observed maximum plasma concentration (Tmax)
- Terminal disposition phase rate constant (lambdaz)
- Terminal phase phase half-life (t1/2)
- Apparent oral clearance (CL/F)
- Apparent terminal phase volume of distribution (Vz/F)
- Accumulation ratio

For PK data acquired in the Mutual DDI PK Expansion Cohort an analysis of variance will be performed with log-transformed C_{max} and AUC_{τ} as the dependent variables, treatment as the fixed effect, and patient as the random effect. Least-square mean ratios between the treatment states (MLN0128+ MLN1117 [Test]) versus MLN0128 or MLN1117 alone [Reference]) will be calculated along with 90% confidence intervals (CIs). The chosen schedule for the mutual DDI PK expansion cohort was MLN1117 and MLN0128 both Administered MTuW (cohort B). A comparison will be made of MLN0128 (C1D3) alone versus MLN0128+MLN1117 (C1D10) and MLN1117 alone (C1D17) versus MLN0128+MLN1117 (C1D10).

In the Mutual DDI PK Expansion Cohort the amount of MLN0128 and MLN1117 excreted in urine will be determined based upon urine concentration of each agent and the cumulative volume of urine collected during the 0-8h collection duration, as specified in the protocol.

The renal clearance of MLN0128 and MLN1117 will be determined by the taking the ratio of amount of MLN0128 and MLN1117 excreted in urine from 0-8h post-dose to the plasma AUC0-8h. These parameters will be listed and summarized for the mutual DDI PK expansion cohort.

7.9.2 Pharmacodynamic Analysis

Company Confidential Information

[redacted]

7.9.2.1 Pharmacodynamic Parameter Determination

Non-compartmental analysis will be used to determine the pharmacodynamic parameters using Company Confidential Information [redacted] for all pharmacodynamic evaluable subjects in arms B and C

only. The analysis will be based on the percent change from baseline in the H- score and the actual sampling times.

The following parameters will be calculated for each marker:

- Emax: Maximum observed effect
- TEmax: Time of maximum observed effect (hours)
- AUEC0-t: Area under the effect (inhibition)-time curve over the dosing interval (t=8 or 24 hrs based on available data), calculated using the linear trapezoidal rule

The pharmacodynamic parameters will be summarized by MLN0128/MLN1117 schedule for each arm (B and C only). Scatter plots of individual and median values of AUEC0-t vs. MLN0128/MLN1117 schedule will be generated for each arm (B and C only) and for each marker.

7.10 Other Outcomes

7.10.1 Pharmacogenomic Analysis

DNA extracted from blood samples obtained from all patients at screening may be evaluated for germline polymorphisms in CYP2C9 and CYP2C19 genes and may also be used to assess the impact of genetic polymorphisms on clinically important drug transporters, such as BCRP, OATP1B1, or OATP1B3, if either MLN0128 or MLN1117 is determined to be substrates of these transporters in future studies. Data from this study may be combined with data from previous and/or future studies to explore the relationship between MLN0128 and MLN1117 PK and the CYP2C9 and CYP2C19 genotypes. DNA samples may be used as a comparator and evaluated for mutations detected in tumor samples.

The results of such analysis will not be presented in the CSR but as a standalone report.

7.11 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results.

These analyses will be performed using the safety population.

7.11.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0. Treatment-emergent AEs are defined as any AE that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study medication. Treatment-emergent AEs will be tabulated by MedDRA system organ class and preferred term and will include the following categories

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs.
- The most commonly reported treatment-emergent AEs [by preferred term – at least 10% of patients in each treatment arm in the dose escalation cohort, and for at least 10% of patients in the DDI expansion cohort.]

TEAEs will be summarized by by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort.

Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, and once within each preferred term.

Adverse events of interest will be tabulated for the following:

Adverse event of interest	MedDRA Preferred Term
Rash	Fixed eruption, Mucocutaneous rash, Rash, Rash generalized, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash rubelliform, Rash scarlatiniform, Rash vesicular, Dermatitis exfoliative, Drug eruption, Drug hypersensitivity, Drug rash with eosinophilia and systemic symptoms, Reaction to drug excipients, Toxic skin eruption, Administration related reaction, Erythema, Generalised erythema, Rash erythematous, Rash popular, Rash papulosquamous

Adverse event of interest	MedDRA Preferred Term
Renal Insufficiency (MedDRA Standardized Medical Query)	Acute phosphate nephropathy , Acute prerenal failure (Narrow), Anuria (Narrow), Azotaemia (Narrow), Continuous haemodiafiltration (Narrow), Dialysis (Narrow), Haemodialysis (Narrow), Neonatal anuria (Narrow), Nephropathy toxic (Narrow), Oliguria (Narrow), Peritoneal dialysis (Narrow), Prerenal failure (Narrow), Renal failure (Narrow), Renal failure acute (Narrow), Renal failure neonatal (Narrow), Renal impairment (Narrow), Renal impairment neonatal (Narrow), Albuminuria (Broad), Blood creatinine abnormal (Broad), Blood creatinine increased (Broad), Blood urea abnormal (Broad), Blood urea increased (Broad), Blood urea nitrogen/creatinine ratio, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Creatinine urine abnormal (Broad), Creatinine urine decreased (Broad), Crystal nephropathy (Broad), Glomerular filtration rate abnormal, Glomerular filtration rate decreased, Hypercreatininaemia (Broad), Nephritic syndrome (Broad), Nephritis (Broad), Oedema due to renal disease (Broad), Protein urine present (Broad), Proteinuria (Broad), Renal function test abnormal (Broad), Renal transplant (Broad), Renal tubular disorder (Broad), Renal tubular necrosis (Broad), Tubulointerstitial nephritis (Broad), Urea renal clearance decreased (Broad), Urine output decreased (Broad)
Mucosal Inflammation	Burning sensation mucosal, Mucosal erosion, Mucosal excoriation, Mucosal exfoliation, Mucosal hyperaemia, Mucosal inflammation, Mucosal necrosis, Mucosal ulceration, Aphthous stomatitis, Mouth ulceration, Oral mucosa erosion, Stomatitis, Stomatitis haemorrhagic, Stomatitis necrotizing, Oral discomfort, Oral mucosal blistering, Oral mucosal erythema, Oral mucosal exfoliation, Oropharyngeal blistering, Oropharyngeal discomfort, Oropharyngeal pain
Asthenic Conditions	Asthenia, Fatigue, Lethargy, Listless, Malaise, Sluggishness, Muscle Weakness

7.11.1.1 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment emergent serious AE (SAE) will be summarized by MedDRA system organ class, and preferred term. Drug-related SAEs will be summarized similarly.

7.11.1.2 Deaths

A by-subject listing of the deaths will be presented. An on-study death is defined as a death that occurs between the first dose of study drug and within 30 days of the last dose of study drug.

7.11.1.3 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of subjects experiencing treatment emergent AEs resulting in discontinuation of study drug will be summarized by MedDRA system organ class, and preferred term.

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

7.11.1.4 Dose Limiting Toxicities (DLTs)

A by-subject listing of DLTs in Cycle 1 will be presented for patients in the DLT-evaluable population.

7.11.2 Clinical Laboratory Evaluations

For the purposes of summarization, all laboratory values will be converted to standardized units. Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE version 4.0.

The number and percent of patients with shifts in the worst post-baseline NCI CTCAE toxicity grade relative to the baseline toxicity grade will be summarized:

Chemistry	Hematology
Alanine aminotransferase (ALT) increased	Hemoglobin
Alkaline phosphatase increased	Activated partial thromboplastin time (aPTT) prolonged
Aspartate aminotransferase (AST) increased	INR increased
Bilirubin (total) increased	Lymphocyte count decreased
Cholesterol high	Lymphocyte count increased
Creatinine increased	Neutrophil count decreased
Calcium decreased	Platelet count decreased
Calcium increased	White blood cell count decreased

Chemistry	Hematology
Gamma glutamyl transferase (GGT) increased	
Glucose decreased	
Glucose increased	
Potassium decreased	
Potassium increased	
Magnesium decreased	
Magnesium increased	
Sodium decreased	
Sodium increased	
Triglycerides increased	
Albumin increased	
Phosphate increased	

For those laboratory tests not assigned NCI-CTCAE toxicity grades the number and proportion of patients with shifts in laboratory values to outside the laboratory normal range relative to the baseline value will be summarized.

Laboratory data will be summarized by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort.

7.11.3 Vital Signs

Vital sign results (diastolic and systolic blood pressure) and body weight will be summarized as follows:

- Baseline value
- Minimum post-baseline value
- Change to Minimum post-baseline value
- Maximum post-baseline value
- Change to Maximum post-baseline value

Vital signs data will be summarized by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort.

7.11.4 12-Lead ECGs

Selected ECG parameters (ventricular rate, PR, QRS, QT, and QTc (Fridericia) will be summarized as follows:

- Baseline value
- Minimum post-baseline value
- Change to Minimum post-baseline value
- Maximum post-baseline value
- Change to Maximum post-baseline value

All QT values will be converted to QTcF using Fridericia's correction:

$$QT_F = \frac{QT}{\sqrt[3]{RR}}(\text{sec})$$

[Note: RR = 60 seconds/ventricular rate in beats/minute]

The change from baseline in QT/QTc interval and the number and percent of subjects with increases >30 ms and >60 ms will be summarized.

ECG data will be summarized by MLN0128/MLN1117 dose level within each of the treatment arms, total for each treatment arm, total for the dose escalation cohort, and for the mutual DDI PK expansion cohort.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

No formal interim analysis is planned. In the Expansion Stage, the first stage of Simon Two Stage Design will be used to make a go-no go decision.

7.13 Changes in the Statistical Analysis Plan

The planned interim analysis was not performed as patients were not enrolled in the tumor-specific cohorts in the Expansion Stage planned in the protocol.

Mean laboratory values over time were not plotted for key lab parameters as specified in the statistical methods section of the protocol.

8.0 OTHER

The below subject-level listings will be generated:

- Disposition
- Populations
- Demographics
- Baseline Characteristics
- Prior Therapy
- Prior Radiation
- Exposure to study drug
- All Adverse events
- TEAEs leading to study drug discontinuation
- Serious AEs
- On-study deaths
- DLTs during Cycle 1
- Pharmacokinetic concentrations
- Pharmacokinetic parameters
- Pharmacodynamic data
- Efficacy