Title: A Phase I, Open Label, Dose Escalation Study of Oral Administration of Single Agent INK128 in Subjects with Advanced Malignancies Followed by an Expansion in Subjects with Measurable Disease

NCT Number: NCT01058707

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STATISTICAL ANALYSIS PLAN

A Phase I, Open Label, Dose Escalation Study of Oral Administration of Single Agent INK128 in Subjects with Advanced Malignancies Followed by an Expansion in Subjects with Measurable Disease

Protocol #: INK128-001

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	adverse event
AUC	area under the curve
Cmax	maximum concentration
Ctrough	Trough concentration
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MTD	maximum tolerated dose
N	number of subjects
NCI	National Cancer Institute
ORR	objective response rate
PD	pharmacodynamic
PK	Pharmacokinetic
PR	partial response
QD	Once daily
QW	Once weekly
RECIST	Response Criteria for Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
$T_{1/2}$	half-life
Tmax	time of maximum concentration
TEAEs	treatment emergent adverse events
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the statistical analysis plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will addresses the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This is a phase 1, open-label study that consists of a dose escalation phase in subjects with advanced malignancies, followed by an expansion phase of safety and efficacy in up to 80 additional response-evaluable subjects with measurable disease. Up to 4 different dosing schedules will be explored in the dose escalation phase: QD, once weekly (QW), QDx3d QW, and QDx5d QW. Enrollment will start with the once daily schedule. Once the MTD for this schedule is identified, enrollment will begin in parallel in the alternate dosing schedules. Once the MTD has been identified for each of the 4 dosing schedules evaluated, an additional 6 subjects may be enrolled in 1 or more of the dosing schedules to gain further PK and safety data prior to the expansion phase of the study.

Based on biochemical data, available PK, and tolerability data for each MLN0128 dosing schedule, along with potential early signs of anti-tumor activity from subjects treated during the dose escalation phase, 1 or more dosing schedules will be selected to be evaluated in the expansion phase. In the expansion phase, the safety and efficacy of 1 or more MLN0128 treatment schedules will be evaluated in parallel in a renal tumor-specific cohort, as well as in cohorts of selected tumor types (endometrial and bladder cancers) for a total of 80 response-evaluable subjects.

1.2 Study Objectives

The primary objectives of the study are:

- To determine the MTD and DLT of oral administration of MLN0128 given daily or via alternate dosing schedules in subjects with advanced malignancies

- To evaluate the safety and tolerability of orally administrated single-agent MLN0128, given daily or via alternate dosing schedules, in both the dose escalation and the expansion phases of the study

The secondary objectives of the study are:

- To evaluate the plasma PK of single-agent MLN0128 following oral administration daily and according to alternate dosing schedules, in subjects with advanced malignancies
- To evaluate the pharmacodynamic effect of MLN0128 activity in surrogate tissue (skin) and tumor as measured by S6, eukaryotic initiation factor 4E-binding protein 1 (4EBP1), and AKT, as well as in peripheral blood cells as measured by 4EBP1
- To evaluate preliminary anti-tumor activity of MLN0128

The exploratory objectives of the study are:

CCI

[redacted]

2. POPULATIONS FOR ANALYSIS

2.1 All Subjects as Treated (ASaT) Population

The ASaT population consists of all enrolled subjects who receive at least 1 dose of MLN0128. The All Subjects as Treated (ASaT) population will be used for the analysis of safety data.

2.2 Response-Evaluable Population

The response-evaluable population includes subjects who receive at least 1 dose of MLN0128 dose, have measurable disease at baseline, and undergo at least 1 post-baseline disease assessment. Subjects who do not have at least 1 post-baseline disease assessment but discontinued study drug due to symptomatic and/or clinical deterioration will be included in the response-evaluable population.

2.3 Pharmacokinetics Population

The PK population consists of all subjects enrolled during the dose escalation phase of the study who receive at least one dose of MLN0128 and have sufficient concentration-time data to calculate one or more PK parameters.

2.4 Pharmacodynamics Population

The PD population consists of all subjects enrolled during the dose escalation phase with at least one pre and post treatment peripheral blood, tumor biopsy, or skin biopsy sample collected. Analyses of p4EBP1 from peripheral blood samples and p4EBP1, pAKT, pS6, pNDRG1, and pPRAS40 from skin and tumor biopsies will be performed using the PD population.

2.5 Dose-Escalation Evaluable Population

The dose-escalation evaluable population is defined as subjects who received 75% or more of planned doses of MLN0128 in Cycle 1 or stopped study drug before receiving 75% of planned doses because of study drug related AE (considered as a DLT). Per the protocol during the dose escalation phase, subjects who receive at least 75% (21 of 28 for QD dosing schedule; 3 of 4 for QW dosing schedule; 9 of 12 for QDx3d QW dosing schedule; 15 of 20 for QDx5d QW dosing schedule) of the planned doses in Cycle 1 will be considered to have sufficient safety data/follow-up to support dose escalation. Subjects who withdraw from

study before receiving 75% of the planned doses in the first cycle of treatment for reasons unrelated to study drug toxicity will be considered to have inadequate data to support dose escalation.

The dose-escalation evaluable population will be used for the analysis of DLTs.

3. HYPOTHESES AND DECISION RULES

Not applicable in a phase 1 study.

4. INTERIM ANALYSIS

Not applicable.

5. STATISTICAL METHODOLOGY

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 nonmissing) per category for categorical data, unless specified otherwise. Unless noted otherwise data from the dose escalation phase will be summarized by schedule and dose level [ordered] and data from the expansion phase will be summarized as follows:

1. Disposition/Demographics/Baseline/Characteristics/Prior Therapy/AE/ECG/Vitals/ConMeds:

Cohort: Renal							
TORC1 Naïve				TORC1 Failure			
5 mg QD	30 mg QW	40mg QW	Total	5 mg QD	30 mg QW	40mg QW	Total

Cohort: Endometrial/Bladder							
Endometrial				Bladder			
5 mg QD	30 mg QW	40mg QW	Total	5 mg QD	30 mg QW	40mg QW	Total

2. Efficacy:

Cohort: Renal							
TORC1 Naïve				TORC1 Failure			
5 mg QD	30 mg QW	40mg QW	**Total QW**	5 mg QD	30 mg QW	40mg QW	**Total QW**

Cohort: Endometrial/Bladder							
Endometrial				Bladder			
5 mg QD	30 mg QW	40mg QW	**Total QW**	5 mg QD	30 mg QW	40mg QW	**Total QW**

5.1 Sample Size Justification

Dose Escalation Phase

Cohorts of 3 to 6 subjects will be enrolled in each MLN0128 dose cohort and dose schedule evaluated based on a standard phase 1 sequential dose escalation scheme. Additional subjects, up to a total of 12, may be enrolled in a given cohort and schedule to better understand the safety profile and tolerability of a particular dose level/dose schedule combination. Each subject will participate in only 1 dose cohort/dose schedule. The total number of subjects to be enrolled in the dose escalation phase of the study is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD for each dose schedule evaluated.

Expansion Phase

Based on safety and available PK data of MLN0128 along with possible early signs of antitumor activities from subjects treated during the dose escalation phase, the expansion phase of the study will evaluate 1 or more populations (initially 2) with measurable disease: renal cell cancer and a cohort of selected tumor types (endometrial and bladder cancers). Cohorts may enroll subjects in parallel in the expansion phase, each with 15 to 25 response-evaluable subjects. The smaller sample size of 15 response-evaluable subjects per disease cohort is based on following considerations: A single agent that results in an objective response rate of 1% or less is considered to have insufficient activity to warrant further study. An objective response rate of 20% or greater is considered sufficient to warrant further study of the agent. Fifteen subjects per cohort will provide 83% power to detect a statistically significant difference between the uninteresting and interesting objective response rates based on the exact 1-sample binomial test and 1-sided significance level of 5%.

5.2 Randomization and Stratification

Not applicable.

5.3 Unblinding

Not applicable.

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. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

5.4.2 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration.

5.4.3 Windowing of Visits

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

5.5 Subject Disposition

The number of subjects enrolled, in each analysis population, and the reason study drug was discontinued will be summarized for the dose escalation phase by schedule and dose level [ordered] and for the expansion phase as shown in Section 5.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

The following demographic characteristics will be summarized for the dose escalation phase (all subjects) and for the expansion phase as shown in Section 5: age, sex, ethnicity, race, weight, and baseline ECOG performance status.

5.6.2 Medical History

5.6.2.1 General Medical History

Non-Cancer Medical History will be in a by-subject listing.

5.6.2.2 Disease-Specific History

The following disease specific endpoints will be summarized for the dose escalation phase (all subjects) and for the expansion phase as shown in Section 5:

- Type of cancer at diagnosis
  - Breast cancer
    - ER+ and/or PR+/HER2-
    - ER+ and/or PR+/HER2+
    - ER-/PR-/ HER2+
    - ER-/PR-/ HER2-

    [HER2+ is defined as IHC 3 or FISH positive]
  - Lung cancer: Small Cell and NSCLC
- Years since initial diagnosis
- Stage of disease at initial diagnosis
- Stage of disease at study entry
- Years since initial metastatic diagnosis or diagnosis of locally advanced inoperable cancer

The number and percentage of subjects with prior surgery, prior radiation, and prior systemic anticancer therapies will be summarized for the dose escalation phase (all subjects) and for the expansion phase as shown in Section 5. The following will be summarized for those subjects with prior systemic therapies:

- Systemic regimen received (e.g. antibody therapy, hormonal therapy)
- Number of prior systemic treatment regimens
- Setting of most recent systemic treatment
- Best response to most recent systemic treatment
- Reason most recent systemic treatment discontinued
- Months on most recent systemic treatment

A scatter plot of the duration of treatment with MLN0128 versus the duration on the most recent systemic treatment (in months) will be generated for each renal expansion cohort (TORC1 Naïve and TORC1 Failure, different symbols for schedule and dose level).

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2013 version). The number and percentage of subjects taking concomitant medications will be tabulated by ATC classification and generic name in the ASaT population by schedule and dose level [ordered] for the dose escalation phase and for the expansion phase as shown in Section 5.

5.7.2 Study Treatments

MLN0128 will be administered orally once in the morning with a meal at approximately the same time of day. Cycles are repeated every 28 days.

- QD dosing schedule: once daily in the morning on Days 1 through 28 of each cycle;

- QW dosing schedule: once in the morning on Days 1, 8, 15, and 22 of each cycle;
- QD×3d QW dosing schedule: once in the morning on Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24 of each cycle;

- QD×5d QW dosing schedule: once in the morning on Days 1, 2, 3, 4, 5, 8, 9, 10, 11,12, 15, 16, 17, 18, 19, 22, 23, 24, 25, and 26 of each cycle.

5.7.2.1 Extent of Exposure

The overall duration of study drug administration (weeks: date of last dose – date of first dose + 1/ 7), total number of cycles administered (distribution and summary statistics), cumulative dose, dose per administration, and percentage of planned original dose will be summarized by schedule and dose level [ordered] for the dose escalation phase and for the expansion phase as shown in Section 5.

The percentage of planned original dose is calculated as the cumulative dose taken (mg) divided by the total planned dose (mg). The total planned dose is:
dose level at study start * doses per week * 4 weeks/cycle * maximum no of cycles.

The number and proportion of subjects with one or more dosage modifications will be tabulated along with the reason for dosage modification. The number and proportion of subjects with intra-patient dose escalation will be summarized

The Cycle 1 compliance is used in the determination of the DLT evaluable population and is calculated as the cumulative dose taken during Cycle 1 (mg) divided by the expected dose in Cycle 1. The expected dose in cycle 1 is:
dose level at study start * doses per week * 4 weeks/cycle

5.8 Efficacy Analyses

The number and percent of subjects in each response category, the objective response rate (CR + PR), clinical benefit rate (CR + PR + SD), best response of SD <6 months, best response of SD ≥6 months will be presented by schedule and dose level [ordered] for the escalation phase and for the expansion phase as shown in Section 5. In addition, for the expansion phase the percentage of subjects with any decrease in the sum of the longest diameters from baseline will be summarized. The objective response rate will be based on the subject's best overall tumor response documented during the course of protocol therapy. The duration of stable disease will be calculated relative to Study Day 1 for those subjects with a best response of stable disease and will be included in a data listing.

The duration of objective response will be calculated for subjects who achieve objective response and will be included in a data listing. For such subject, the duration of objective response is defined as the number of days from the start date of CR, or PR (whichever response is achieved first) to the first date that progressive disease is objectively documented. Those subjects who did not progress are censored at the date of the last response assessment.

Tumor marker data will be included in a data listing.

5.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

5.9.1 Pharmacokinetic Analyses

The pharmacokinetic analyses will be based on PK data collected during the dose escalation portion of the study. Sparse PK data collected during the expansion cohort will be in a data listing. The sparse pharmacokinetic sampling in the expansion cohort will be used as part of the population PK modeling in a separate report.

5.9.1.1 PK Parameters for MLN0128

Data permitting the following PK parameters may be estimated and reported:

Parameter	Definition	Units
C_{max}	Observed maximum concentration	ng/mL
T_{max}	First time Cmax is observed	hr
C_{trough}	Observed concentration at the end of the dosing interval	ng/mL
AUC_{8hr}	Area under the concentration-time curve, from time 0 to 8 hr, estimated using the linear-log trapezoidal method	hr*ng/mL
AUC_{24hr}	Area under the concentration-time curve, time 0 to 24 hr	hr*ng/mL

Parameter	Definition	Units
	sample, estimated using the linear-log trapezoidal method	
$lambda_z$	Terminal disposition phase rate constant. The presence of at least three points in the terminal phase, an r^2 greater than 0.80, and a span equal to or greater than 1.5 are required to report $lambda_z$ and the other PK parameters that are calculating using $lambda_z$.	1/hr
$t_{1/2}$	Terminal disposition phase half-life	hr
AUC_{inf}	Area under the concentration-time curve, time 0 extrapolated to infinity, estimated using the linear-log trapezoidal method.	hr*ng/mL
CL/F	Apparent clearance, extravascular dosing	L/hr
Vz/F	Apparent terminal phase volume of distribution, extravascular dosing	L
Rac_{24hr}	Accumulation ratio based on AUC_{8hr}	unitless

5.9.1.2 **Pharmacokinetic Analyses**

All PK analyses will be performed using the pharmacokinetic population.

Pharmacokinetic Concentrations

Descriptive statistics (number of subjects, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, median, minimum, and maximum) will be used to summarize the plasma concentrations by dosing schedule, dose level and scheduled time. 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 for each dosing schedule, and dose level. Linear and semi-logarithmic plots of individual plasma concentration versus actual sampling time will be provided for each dosing schedule, and dose level.

All individual subject plasma concentration data will be listed.

Pharmacokinetic Parameters

PK parameters will be estimated using non-compartmental methods with WinNonlin® Professional Version 6.1 or higher (Pharsight Corp., Mountain View, CA). The plasma PK parameters will be estimated from the concentration-time profiles for all PK population subjects. 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 subjects, 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 by dosing schedule, and dose level. For T_{max}, only median, minimum value, and maximum value will be presented.

An analysis of dose proportionality will be performed for the PK parameters AUC_{inf}, and C_{max}.

5.9.2 Pharmacodynamic Analyses

Peripheral Blood Cells

Due to issues with assay validation p4EBP1 results will be in a listing but not summarized.

Skin and Tumor Biopsies

Descriptive statistics will be used to summarize baseline, cycle 1 2-4 hour post dose, and the percent change from baseline [((post – pre)/ pre) * 100] for p4EBP1, pAKT, pS6, and pNDRG1 by schedule and dose level [ordered] for the escalation phase. Scatter plots of individual and mean values of the percent change from baseline vs. dose level will be generated for each schedule and biomarker.

Due to issues with staining the pPRAS40 results will be in a listing but not summarized.

5.10 Safety Analyses

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

These analyses will be performed using the ASaT population.

5.10.1 Adverse Events

5.10.1.1 Adverse Events

Treatment emergent adverse events are defined as adverse events that start on or after the first administration of study drug and less than or equal to 30 days after the last administration of study drug. Missing and partially missing adverse event start dates will be imputed according to the specifications described in Section 7.2.7. The reported adverse event term will be assigned standardized terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

All adverse event tabulations will be by schedule and dose level [ordered] for the escalation phase and for the expansion phase as shown in Section 5. Treatment emergent adverse events will be summarized based on the number and percentage of subjects experiencing events by MedDRA system organ class and preferred term. Tabular summaries of the following treatment emergent adverse events will be provided:

- All TEAEs
- TEAEs related to Study Drug
- Grade 3 or greater TEAEs
- Grade 3 or greater TEAEs related to Study Drug
- Most common (at least 2 subjects) TEAEs by maximum severity grade based on NCI-CTCAE (version 4.0) [within each schedule in the escalation, and within each tumor type in the expansion phase]

The number of subjects with a DLT in Cycle 1 will be presented by schedule and dose level [ordered] for the escalation phase based on the dose-escalation evaluable population. Multiple concurrent adverse events leading to DLT will be considered a single DLT.

Adverse events of interest will be tabulated for the following:

Adverse event of interest	MedDRA Preferred Term
Hyperglycemia	Glucose tolerance impaired, Hyperglycaemia, Impaired fasting glucose
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,

Adverse event of interest	MedDRA Preferred Term
	Administration related reaction, Erythema, Generalised erythema, Rash erythematous, Rash popular, Rash papulosquamous
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

5.10.1.2 **Serious Adverse Events**

The number and percentage of subjects experiencing at least 1 treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class and preferred term:.

- Serious TEAEs
- Serious TEAEs related to Study Drug

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

5.10.1.3 **Deaths**

A listing of fatal TEAEs that occur within 30 days of the last administration of study drug will be generated.

5.10.1.4 **Adverse Events Resulting in Discontinuation of Study Drug**

The following listings of TEAEs will be generated:

- TEAEs resulting in discontinuation of study drug
- TEAEs resulting in modification or interruption of study drug

5.10.2 **Laboratory Data**

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. Whenever available, laboratory values will be assigned toxicity grades using the NCI-CTCAE version 4.0. These criteria may include qualifying definitions (e.g., clinical adverse event and/or requirement for concomitant medication) in addition to the specific laboratory value in the definition of the toxicity grades for some laboratory tests. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades. The number and proportion of subjects with shifts in CTCAE toxicity grades relative to the baseline toxicity grade will be summarized by schedule and dose level [ordered] for the escalation phase and for the expansion phase as shown in Section 5.

For those laboratory tests not assigned NCI-CTCAE toxicity grades the number and proportion of subjects with shifts in laboratory values to outside the laboratory normal range relative to the baseline value will be summarized by schedule and dose level [ordered] for the escalation phase and for the expansion phase as shown in Section 5. The NCI-CTCAE version 4.0 toxicity criteria for creatinine will be modified to exclude the comparison to baseline.

5.10.3 Vital Signs

Vital sign results (diastolic and systolic blood pressure) and body weight will be summarized descriptively by schedule and dose level [ordered] for the escalation phase and for the expansion phase as shown in Section 5 as follows:

- Baseline value
- Minimum post-baseline value
- Maximum post-baseline value

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

5.10.4 Electrocardiogram

Selected ECG parameters (ventricular rate, PR, QRS, QT, and QTc (Fridericia)) will be summarized in the same manner as described for vital signs in Section 5.10.3. All QT values will be converted to QTcF using Fridericia's correction:

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

[Note: convert RR recorded on ECG CRF from msec to sec, if the RR is not available use: 60 seconds divided by the 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. Shifts from baseline to maximum post baseline QTcF values will be summarized based on the following categories:
≤ 450 ms, > 450-480 ms, > 480-500 ms and >500 ms.

5.10.5 ECOG Performance Status

ECOG performance status scores will be summarized in the same manner as described for vital signs in section 5.10.3 (maximum post-baseline only).

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Reference materials for this statistical plan include Clinical Study Protocol INK128-001 Amendment 16 dated 3July2013.

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.1 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Subject populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

Treatment-emergent AEs are defined in Section 5.10.1.1.

7.2.1 Study Drug

The term "study drug" represents MLN0128.

7.2.2 Study Day 1

Study Day 1 corresponds to the date of the first dose of study drug. For subjects who receive 1 or more doses of study drug, the start date recorded on the Study Drug Administration (Cycle 1 – Day 1) CRF will be used to determine Study Day 1.

7.2.3 Study Day

Study Day represents the elapsed number of days from Study Day 1, inclusive.

Study Day *n* = (Date of assessment – Date of Study Day 1) + 1 day

Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to Study Day 1. Study Day −1 will be the day before Study Day 1, and in general, negative days will be measured backwards starting from Study Day −1.

7.2.4 Cycle k Day j

The first 28-day treatment cycle will begin with the first dose of study drug, and will be denoted as "Cycle 1 Day 1". In general, the start date of each cycle (i.e., Day 1 of Cycle *k*, where *k*=1 to maximum number of cycles started) equals the date of the first dose of study drug administered in the corresponding cycle.

Day *j* represents the elapsed number of days since the first dose of protocol therapy in Cycle *k* and Day *j* = (Date of assessment – Date of Day 1 in Cycle *k*) + 1. Unless otherwise specified, the timing of study-related visits and assessments will be calculated relative to Day 1 in each cycle.

7.2.5 Age at Screening

Age will be calculated in years relative to the date the informed consent is signed based on the following SAS programming statement:

Age = floor ((intck ('month', birthdt, icdt) – (day (icdt) < day (birthdt))) / 12);

For subjects whose day and month of birth may not be available due to confidentiality agreements, age (and any other variables where this information is needed) will be calculated assuming a birth day and month of July 1st.

7.2.6 Incomplete Adverse Event Start Dates

Missing and incomplete adverse event start dates will be imputed based on the algorithm described below. The algorithm will be used only if the end date of the adverse event (if reported) indicates the event was not resolved before the first administration of study drug. The purpose of the imputation is to determine if an adverse event with a missing or incomplete start date is treatment emergent (as defined in Section 5.10.1.1).

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 MLN0128 and on or before the month and year of the date of the last dose of MLN0128 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 MLN0128 and on or before the year of the date of the last dose of MLN0128 plus 30 days.

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

8. REFERENCES

Not applicable.