



Title: A Phase I, Open Label, Dose Escalation Study of Oral Administration of INK128 in Combination with Paclitaxel, with/without Trastuzumab, in Subjects with Advanced Solid Malignancies

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- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

# STATISTICAL ANALYSIS PLAN

A Phase I, Open Label, Dose Escalation Study of Oral  
Administration of INK128 in Combination with Paclitaxel,  
with/without Trastuzumab, in Subjects with Advanced Solid  
Malignancies

Protocol #: INK128-003

SAP Version:  
Final

Date of Statistical Analysis Plan:  
7October2013

## Approval Signatures

7 October 2013  
Date

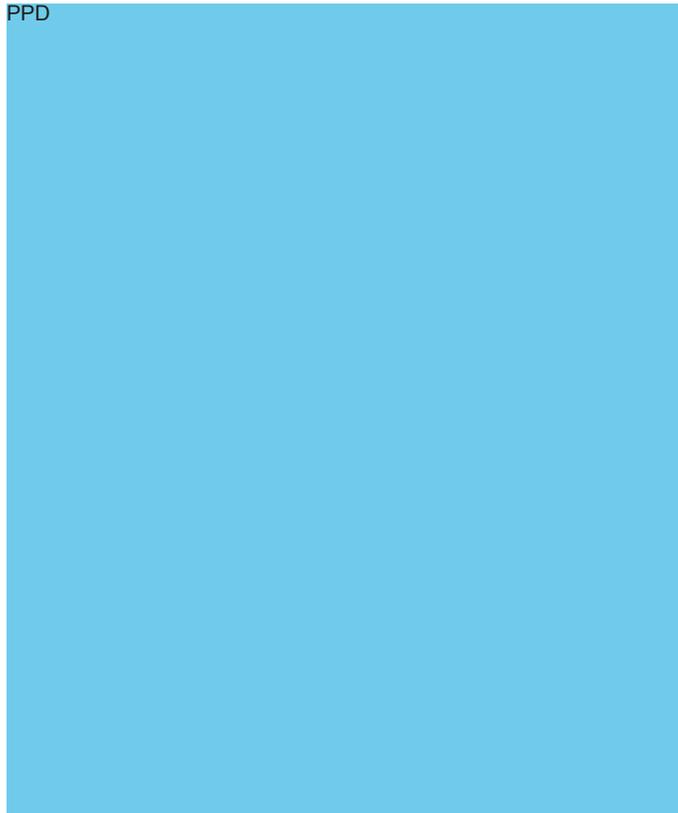
7 October 2013  
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Date

8 October 2013  
Date

PPD



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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Term</b>	<b>Definition</b>
CCI	
AE	adverse event
CCI	
ASaT	All Subjects as Treated
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
HER2	Human Epidermal Growth Factor Receptor 2
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MTD	maximum tolerated dose
N	number of subjects
NCI	National Cancer Institute
CCI	
ORR	objective response rate
PD	pharmacodynamic
PK	Pharmacokinetic
PR	partial response
PRAS40	proline rich AKT substrate of 40 kD
QD	Once daily
QW	Once weekly
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

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<b>Abbreviation or Term</b>	<b>Definition</b>
SE	standard error
S6	ribosomal protein
T <sub>1/2</sub>	half-life
T <sub>max</sub>	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 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 a phase 1, open-label study consisting of a dose-escalation phase in advanced solid malignancies to determine the MTD of oral administration of MLN0128 (QDx3dQW on a 4-week cycle) or via alternate dosing schedules (such as 5 days on, 2 days off repeated weekly [QDx5d QW] or QW) in combination with an infusion of paclitaxel on Days 1, 8, and 15 of each cycle (MLN0128P), followed by an expansion phase at the MLN0128P MTD ( $MTD^{MLN0128P}$ )  $\pm$  trastuzumab in up to 25 additional subjects for further safety and preliminary efficacy. A cycle will be defined as 4 weeks.

Once the  $MTD^{MLN0128P}$  is determined for each of the dosing schedules evaluated, an additional 6 subjects may be enrolled at the  $MTD^{MLN0128P}$  for further safety and PK evaluation. A dose and schedule will be selected for the expansion phase which may enroll subjects into 2 arms in parallel:

- Arm A will consist of HER2- cancer subjects receiving MLN0128P at the  $MTD^{MLN0128P}$
- Arm B will consist of HER2+ cancer subjects receiving MLN0128P at the  $MTD^{MLN0128P}$  plus weekly trastuzumab (MLN0128PH)

### **1.2 Study Objectives**

The primary objectives of the study are:

- To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of MLN0128 when administered on a QDx3d QW schedule of a 4-week cycle or via alternate dosing schedules (such as 5 days on, 2 days off weekly [QDx5d QW]) in

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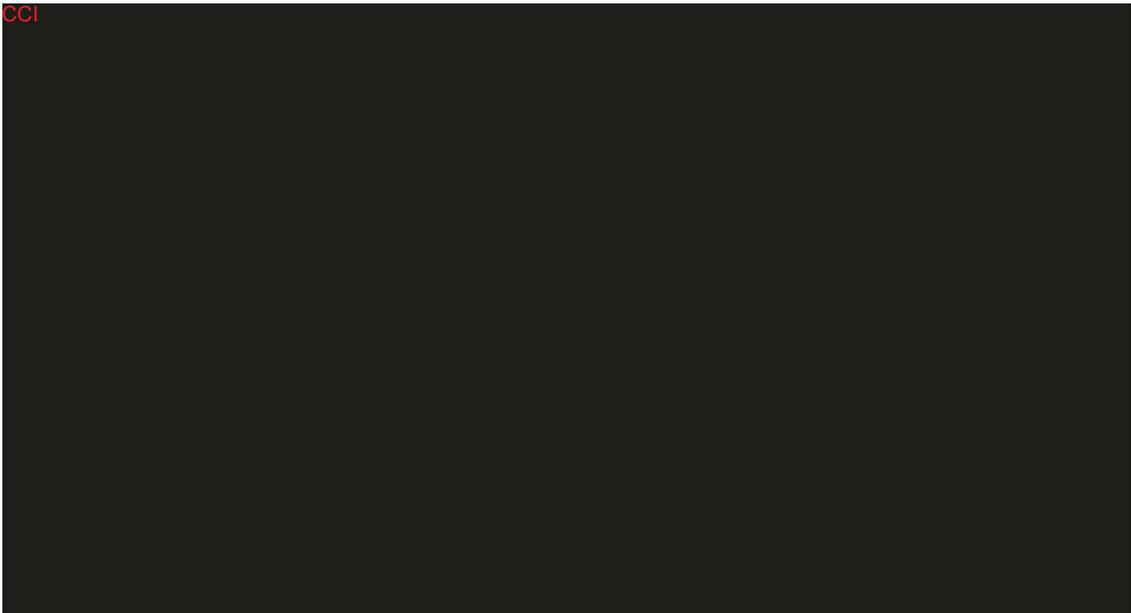
combination with paclitaxel on Days 1, 8, and 15 of each cycle (MLN0128P) in subjects with advanced solid malignancies

- To evaluate the safety and tolerability of oral administration of MLN0128 QDx3d QW of a 4-week cycle or via alternate dosing schedules (such as QDx5d QW) in combination with paclitaxel on Days 1, 8, and 15 of each cycle (MLN0128P) in advanced solid malignancies

The secondary objectives of the study are:

- To evaluate the plasma PK of MLN0128 in combination with paclitaxel
- To evaluate the plasma PK of paclitaxel in combination with MLN0128
- To evaluate the preliminary anti-tumor activity of oral administration of MLN0128 in combination with paclitaxel (MLN0128P)
- To evaluate the safety and preliminary anti-tumor activity of the combination of MLN0128, paclitaxel , and trastuzumab (MLN0128PH) in subjects with HER2+ cancers

The exploratory objectives of the study are:

-  CCI
- 

## **2. POPULATIONS FOR ANALYSIS**

### **2.1 All Subjects as Treated (ASaT) Population**

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

For purposes of defining the MTD and/or expansion phase recommended dose of MLN0128, subjects will be evaluated according to the starting dose level and planned schedule of MLN0128 during the first treatment cycle. For most subjects, this will be the cohort to which they were assigned.

### **2.2 Full Analysis Set (FAS) Population**

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of tumor response and other efficacy-related data. Subjects will be excluded from the FAS for the following reasons:

- Failure to receive at least 1 dose of MLN0128
- No post-baseline endpoint data subsequent to at least 1 dose of MLN0128
- Lack of baseline data for those analyses that require baseline data

### **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 or paclitaxel and have sufficient concentration-time data to calculate one or more PK parameters for either compound.

### **2.4 Dose-Escalation Evaluable Population**

Per the protocol subjects who receive  $\geq 75\%$  of the planned MLN0128 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 at least 75% of the planned MLN0128 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. In such cases, replacement subjects may be enrolled to receive the same starting dose of MLN0128 as the subjects who withdraw prematurely.

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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).

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 specified otherwise summary tables will be presented by schedule and MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- MLN0128P 8 mg QDx3d QW and HER2+ MLN0128P 8 mg QDx3d QW plus Trastuzumab) for the expansion cohort.

Study drug refers to MLN0128, Paclitaxel, or Trastuzumab.

**5.1 Sample Size Justification**

**Dose Escalation Phase**

Cohorts of 3 to 6 subjects will be enrolled in each MLN0128 dose cohort based on a standard phase 1 sequential dose escalation scheme. Each subject will participate in only 1 dose cohort. 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.

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**Expansion Phase**

After the MTD of MLN0128 has been identified, 2 cohorts of subjects will be enrolled in parallel:

- Arm A will consist of approximately 12 to 15 safety-evaluable HER2– cancer subjects receiving MLN0128P
- Arm B will consist of approximately 12 to 15 safety-evaluable HER2+ cancer subjects receiving MLN0128P plus weekly trastuzumab

Per Amendment number 6 the number of subjects was changed from 30 to 12-15.

**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 Patient Disposition**

The number of subjects enrolled, in each analysis population, and the reasons each study drug was discontinued will be presented by schedule and MLN0128 dose level [ordered] for

the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort.

## **5.6 Demographics and Baseline Disease Characteristics**

### **5.6.1 Demographics**

The following demographic characteristics will be summarized for each cohort (escalation, expansion: HER2+, HER2- plus Trastuzumab separately) and all patients: age, sex, ethnicity, race, weight, and baseline ECOG performance status.

### **5.6.2 Medical History**

#### **5.6.2.1 General Medical History**

Medical history findings will be in a by-patient listing.

#### **5.6.2.2 Disease-Specific History**

The following disease specific endpoints will be summarized for each cohort (escalation, expansion: HER2+, HER2- plus Trastuzumab separately) and all patients:

- Years since initial diagnosis
- Diagnosis at study entry
  - 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
  - Expansion only: HER2 status (regardless of tumor type)
- Stage of disease at initial diagnosis
- Years since initial metastatic diagnosis of diagnosis of locally advanced inoperable cancer
- Stage of disease at study entry

The number and percentage of subjects with prior surgery, prior radiation, and prior systemic anticancer therapies will be summarized for each cohort (escalation, expansion: HER2+, HER2- plus Trastuzumab separately) and all patients. 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

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- Reason most recent systemic treatment discontinued

## **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 patients taking concomitant medications will be tabulated by ATC classification and generic name in the ASaT population by schedule and MLN0128 dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort.

### **5.7.2 Study Treatments**

All subjects will receive paclitaxel (80 mg/m<sup>2</sup>) on Days 1, 8, and 15 in combination with MLN0128 given either as QDx3d QW, QDx5d QW, or QW in each 4-week cycle. Once the MTD of MLN0128P is reached in the dose escalation phase, Her2+ cancer subjects enrolled into Arm B of the expansion phase will also receive trastuzumab weekly.

#### **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) and total number of cycles administered (distribution and summary statistics) will be summarized by schedule and MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort. The cumulative dose, dose per administration, and percentage of planned original dose for each drug (MLN0128, Paclitaxel, and Trastuzumab) will be summarized. The number and proportion of subjects with one or more dosage modifications will be tabulated along with the reason for dosage modification for each study drug. For MLN0128 the number and proportion of subjects with intra-patient dose escalation will be summarized.

## **5.8 Efficacy Analyses**

The number and percent of patients 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 MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort. 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

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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

RECIST Progression or Clinical Progression will be counted as progressive disease.

The duration of objective response will be calculated for subjects who achieve objective response and will be included in a data listing. For such subjects, 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.

**5.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis**

**5.9.1 Pharmacokinetic Analyses**

**5.9.1.1 PK Parameters for MLN0128**

The following PK parameters will be estimated as data permit:

<b>Parameter</b>	<b>Definition</b>	<b>Units</b>
$C_{max}$	Observed maximum concentration	ng/mL
$T_{max}$	First time $C_{max}$ is observed	hr
$AUC_{6hr}$	Area under the concentration-time curve, from time 0 to 6 hr, estimated using the linear-log trapezoidal method	hr*ng/mL
$AUC_{24hr}$	Area under the concentration-time curve, time 0 to 24 hr sample, estimated using the linear-log trapezoidal method	hr*ng/mL
$\lambda_{z}$	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
$Rac_{6hr}$	Accumulation ratio based on $AUC_{6hr}$	unitless

### 5.9.1.2 PK Parameters: Paclitaxel

The following PK parameters will be estimated as data permit:

Parameter	Definition	Units
C <sub>max</sub>	Observed maximum concentration	ng/mL
T <sub>max</sub>	First time C <sub>max</sub> is observed	hr
AUC <sub>6hr</sub>	Area under the concentration-time curve, from time 0 to 6 hr, estimated using the linear-log trapezoidal method	hr*ng/mL
AUC <sub>24hr</sub>	Area under the concentration-time curve, time 0 to 24 hr sample, estimated using the linear-log trapezoidal method	hr*ng/mL
lambda <sub>z</sub>	Terminal disposition phase rate constant. The presence of at least three points in the terminal phase, an r <sup>2</sup> greater than 0.80, and a span equal to or greater than 1.5 are required to report lambda <sub>z</sub> and the other PK parameters that are calculating using lambda <sub>z</sub> .	1/hr
t <sub>1/2</sub>	Terminal disposition phase half-life	hr
AUC <sub>inf</sub>	Area under the concentration-time curve, time 0 extrapolated to infinity, estimated using the linear-log trapezoidal method.	hr*ng/mL
CL	Clearance	L/hr
V <sub>ss</sub>	Steady-state volume of distribution	L

### 5.9.1.3 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 compound, 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 compound, dosing schedule, and dose level. Linear and semi-logarithmic plots of individual plasma concentration versus actual sampling time will be provided for each compound, 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<sup>®</sup> 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 compound, dosing schedule, and dose level. For  $T_{max}$ , only median, minimum value, and maximum value will be presented.

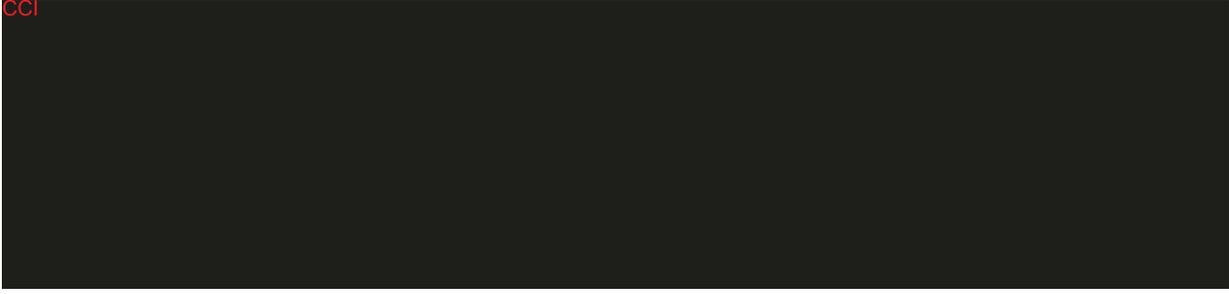
**5.9.2 Pharmacodynamic Analyses**

CCI



### 5.9.3 **Biomarker Analysis**

CCI



### 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, vision examination, vital signs, ECG, and clinical laboratory results.

These analyses will be performed using the safety 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 10.7.2. 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 MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort.

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. Summary tables and listings will be provided by schedule and MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort.

Tabular summaries of the following treatment emergent adverse events will be provided:

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- 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 patients) TEAEs by maximum severity grade based on NCI-CTCAE (version 4.0) [for each schedule in the escalation, and for each arm in the expansion cohort]

The number of patients with a DLT in Cycle 1 will be presented by schedule and MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort (if experienced) based on the dose-escalation evaluable population. The dose-escalation evaluable population includes subjects from the ASaT population who receive at least 75% of the planned doses of MLN0128 in Cycle 1 or stop study drug before receiving 75% of the planned doses because of study drug related AE. 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, 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,

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Adverse event of interest	MedDRA Preferred Term
	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**

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 Study Drug Modifications**

The following listings of TEAEs will be generated:

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- 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 MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort.

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 by schedule and MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort.

**5.10.3 Vital Signs**

Vital sign results (diastolic and systolic blood pressure) and body weight will be summarized descriptively by schedule and MLN0128P dose level [ordered] for the escalation phase and by arm (HER2- and HER2+ plus Trastuzumab) for the expansion cohort 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 Electrocardiograms

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:

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

[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 patients 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 5.10.43 (maximum post-baseline only).

### 6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Reference materials for this statistical plan include Clinical Study Protocol INK128-003 Amendment 6 dated 25March 2013.

The following analyses were planned in the protocol but not included in the statistical analysis plan:

1. Use of per-protocol population as a supportive analysis for tumor response is not relevant for a phase 1 study.
2. The 2- sided 95% exact binomial confidence interval around the estimate of the DLT rate.
3. Adverse incidence rates by cycle.
4. Descriptive statistics for laboratory values at each timepoint.

## **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, Paclitaxel or Trastuzamab.

#### **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  $n = (\text{Date of assessment} - \text{Date of Study Day 1}) + 1$  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 1 Day 1**

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. If study drug is permanently discontinued,

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then the cycle and cycle day for study-related assessments done after the last cycle will be replaced in the tables, figures, and listings with the visit name (eg, Termination Visit). The visit date and study day also will be used to identify the timing of such assessments.

**7.2.5 Cycle  $k$  Day  $j$**

Day  $j$  represents the elapsed number of days since the first dose of protocol therapy in Cycle  $k$ .

$$\text{Day } j = (\text{Date of assessment} - \text{Date of Day 1 in Cycle } k) + 1$$

Unless otherwise specified, the timing of study-related visits and assessments will be calculated relative to Day 1 in each cycle.

As noted previously, if study drug is permanently discontinued, then the cycle and cycle day for study-related assessments done after the last cycle of study drug will be replaced in the tables, figures, and listings with the visit name (eg, Termination Visit). The visit date and study day also will be used to identify the timing of such assessments.

**7.2.6 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:

$$\text{Age} = \text{floor} ((\text{intck} ('month', \text{birthdt}, \text{icdt}) - (\text{day} (\text{icdt}) < \text{day} (\text{birthdt}))) / 12);$$

For patients 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.

**8. REFERENCES**

Not applicable.