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

NCT Number:

Protocol Approve Date: March 5, 2014

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

CLINICAL STUDY PROTOCOL

Study 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
Protocol Number:	INK128-003
Investigational Product:	MLN0128 (formerly INK128)
US IND Number:	104,801
Indication:	Advanced Solid Malignancies
Sponsor:	Millennium Pharmaceuticals, Inc. 40 Landsdowne Street Cambridge, MA USA 02139
Development Phase:	Phase 1
Sponsor's Responsible Medical Officer:	PPD

Original Protocol Date:	January 12, 2011
Amendment 1 Date:	July 15, 2011
Amendment 2 Date:	October 12, 2011
Amendment 3 Date:	April 03, 2012
Amendment 4 Date:	May 21, 2012
Amendment 5 Date:	July 30, 2012
Amendment 6 Date:	March 25, 2013
Amendment 7 Date:	March 5, 2014

Rationale for Amendment 7

The primary purpose of this amendment is to extend the period of contraception duration based on teratogenic and abortive effects identified during preclinical embryofetal studies in rats. Serious adverse event (SAE) and product complaint reporting information has been aligned with current procedures. Additionally, the period of collection of adverse events (AEs) was aligned, and the global clinical lead was updated.

Purposes for Amendment 7

The purposes of this amendment are to:

- Replace PPD as the global clinical lead
- Align the AE collection period in the Schedule of Events with Section 8.3, Monitoring of Adverse Events and Period of Observation, by removing reference to the collection of AEs before initiation of new anticancer therapy
- Extend the period of contraception duration from 30 days to 90 days after the last dose of study drug based on teratogenic and abortive effects identified during preclinical embryofetal studies in rats
- Update SAE reporting information to align with current procedures
- Correct typographical errors, punctuation, grammar, and formatting

For specific examples of changes in text and where the changes are located, see Section 20.4.

Protocol Approval Page

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This protocol amendment has been approved by Millennium Pharmaceuticals, Inc. The following persons are authorized on behalf of Millennium Pharmaceuticals, Inc. to approve this protocol amendment and the signatures below documents this approval.

PPD

Date

PPD

Date

2 SYNOPSIS

TITLE OF STUDY: 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 NUMBER: INK128-003	
STUDY SITES: Multiple centers in the United States (U.S.)	
STUDY PERIOD (MONTHS): Approximately 12 months	**PHASE OF DEVELOPMENT:** Phase 1

OBJECTIVES:

The primary objectives of the study are:

- To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of MLN0128 (formerly INK128) when administered on a 3 days on, 4 days off weekly (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 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 pharmacokinetics (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
- [redacted]

STUDY DESIGN AND PLAN:

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 (QDx3d QW of a 4-week cycle) or via alternate dosing schedules (such as 5 days on, 2 days off repeated weekly [QDx5d QW])

in combination with paclitaxel on Days 1, 8, and 15 of each cycle (MLN0128P), followed by an expansion phase at the MLN0128P MTD ($MTD^{MLN0128P}$) ± trastuzumab 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, A and B, 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)

NUMBER OF SUBJECTS PLANNED:

Cohorts of 3 to 6 subjects with advanced solid malignancies will be enrolled at each MLN0128 dose level evaluated in combination with paclitaxel in 4-week cycles; the exact number of total subjects enrolled will depend on the number of dose levels assessed and the toxicities observed. During dose escalation, subjects who discontinue treatment before completing ≥ 75% of planned MLN0128 doses in Cycle 1 for reasons other than study drug-related toxicity will be replaced. Approximately 15 to 20 safety-evaluable subjects may be enrolled into each arm of the expansion phase. It is estimated that approximately 95 subjects may be enrolled in the entire study.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

Individuals eligible to participate in this study must meet all of the following Inclusion Criteria:

1. Age ≥ 18 years, including males and females;
2. Subjects must have locally advanced or metastatic solid tumors with the exception of primary brain tumor, and have failed or are not eligible for standard of care therapy. Subjects with a history of brain metastasis are eligible for the study as long as they meet all the following criteria: their brain metastases have been treated, they have no evidence of progression or hemorrhage after treatment, have been off dexamethasone for 4 weeks prior to first study drug administration, and they have no ongoing requirement for dexamethasone or anti-epileptic drugs;
3. For Arm A of the expansion phase only, subjects with advanced bladder cancer or endometrial cancer will be enrolled and must have received at least 1, but no more than 2 prior lines of systemic therapy, including adjuvant or hormonal therapy;
4. For Arm B of the expansion phase only, HER2+ cancer is defined as a pathologic diagnosis of cancer which is 3+ by immunohistochemistry (IHC) for HER2 or positive for HER2 gene amplification by fluorescence in situ hybridization (FISH) and subjects must have received at least 1, but no more than 4 prior lines of systemic cytotoxic chemotherapy, excluding adjuvant, hormonal, or targeted therapy;
5. Subjects must have received no more than 4 prior lines of systemic cytotoxic chemotherapy for advanced or metastatic disease;
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1;
7. Subjects must have adequate organ function, including the following:
    a. Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥ 1.5 $x10^9$/L; platelet count ≥ 100 x 10^9/L; hemoglobin ≥ 9 g/dL without transfusion in the last 2 weeks;
    b. Hepatic: total bilirubin ≤ 1.5 x upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) ≤ 2.5 x ULN (<5 x ULN if liver metastases are present);

c. Renal: normal serum creatinine or calculated creatinine clearance ≥ 60 mL/min (Cockroft - Gault formula);

d. Metabolic: fasting serum glucose ≤ 130 mg/dL, and fasting triglycerides ≤ 300 mg/dL;

8. Left ventricular ejection fraction (LVEF) ≥ 5 absolute percentage points below institutional standard of normal as measured by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) within 4 weeks prior to first study drug administration (ie, if the institutional normal is 50%, subject's LVEF may be as low as 45% to be eligible for the study);
9. For women of child-bearing potential, negative serum pregnancy test within 14 days prior to the first study drug administration and use of physician-approved method of birth control from 30 days prior to the first study drug administration to 90 days following the last study drug administration;
10. Male subjects must be surgically sterile or must agree to use physician-approved contraception during the study and for 90 days following the last study drug administration;
11. Ability to swallow oral medications;
12. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures.

Individuals who meet any of the following Exclusion Criteria will not be eligible to participate in the study:

1. Diagnosis of primary brain tumor;
2. Have received prior cancer or other investigational therapy within 2 weeks prior to the first administration of study drug. For prior therapies with a half life longer than 3 days, the interval must be at least 28 days prior to the first administration of study drug and the subject must have documented disease progression. For prior trastuzumab therapy in subjects who enroll in Arm B of the expansion phase, the interval since last prior trastuzumab dose must be at least 7 days;
3. Have initiated hematopoietic growth factors within one week prior to the first administration of study drug; subjects already receiving hematopoietic growth factors on a chronic basis for ≥ 4 weeks are eligible;
4. Chronic systemic corticosteroid (except inhalers) use within one week prior to the first administration of study drug. Premedication with dexamethasone prior to paclitaxel administration in this study is allowed;
5. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128;
6. Poorly controlled diabetes mellitus defined as HbA1c > 7%; subjects with a history of transient glucose intolerance due to corticosteroid administration are allowed in this study if all other inclusion/exclusion criteria are met;
7. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system (CNS) disease, active infection, or any other condition that could compromise the subject's participation in the study;
8. Known human immunodeficiency virus (HIV) infection;
9. Pregnancy (positive serum or urine pregnancy test) or breast feeding;
10. Any history of unstable angina, myocardial infarction, New York Heart Association (NYHA) Class III or IV heart failure (See Appendix C), and/or pulmonary hypertension;
11. Significant active cardiovascular disease including:
    - Uncontrolled high blood pressure (ie, systolic blood pressure >180 mm Hg, diastolic blood

pressure > 95 mm Hg)
- Grade 3 or higher valvular disease
- Grade 3 or higher atrial fibrillation
- Grade 3 or higher bradycardia
- Endocarditis
- Pulmonary embolism
- Recent cerebrovascular accident within 6 months prior to enrollment

12. A requirement for inotropic support or serious uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation) within 1 year prior to screening
13. A pacemaker or implantable cardiac defibrillator
14. Baseline prolongation of the rate-corrected QT interval (QTc) (eg, repeated demonstration of QTc interval > 480 milliseconds) (See Section 7.8.2.2).
15. History of congenital long QT syndrome, ventricular fibrillation, ventricular tachycardia or torsades de pointes

Other Considerations for Exclusion:

Patients taking strong CYP3A4, and CYP2C19 inhibitors and/or inducers should be considered with caution. Alternative treatments that are less likely to affect MLN0128 metabolism, if available, should be considered. If a patient requires treatment with one or more of the strong CYP3A4, and CYP2C19 inhibitors and/or inducers, the medical monitor should be consulted. Examples of the strong CYP3A4 and CYP2C19 inhibitors and inducers include (see Appendix B):

Strong inhibitors:

CYP3A4: ketoconazole, itraconazole, ritonavir, mibefradil, indinavir, clarithromycin

CYP2C19: fluconazole, fluvoxamine, omeprazole, ticlopidine

Strong inducers:

CYP3A4: rifampin (also a moderate CYP2C19 inducer), phenytoin, carbamazepine, St. John's wort

Patients should not consume food or beverages containing the fruit or juice from grapefruits, pomegranates, star fruit, papayas, or Seville oranges within 7 days before first dose of study drug.

INVESTIGATIONAL PRODUCT(S), DOSE, ROUTE AND REGIMEN:

MLN0128 (formerly, INK128) is a mammalian target of rapamycin (mTOR) complex 1 (mTORC1) and mTOR complex 2 (mTORC2) inhibitor currently under clinical investigation. Paclitaxel is an antimicrotubule agent approved by the Federal Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of breast, ovarian, and non-small cell lung cancers. Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2) and is approved by the FDA and EMA for the treatment of breast and gastric cancer with HER2 overexpression. The combinations of MLN0128 and paclitaxel (MLN0128P) during the dose escalation and expansion phase, and MLN0128P plus trastuzumab (MLN0128PH) in Arm B of the expansion phase are considered investigational.

MLN0128 will be supplied in tamper-resistant high density polyethylene bottles as capsules containing 1 mg, 3 mg, or 5 mg dose strengths, which the pharmacist will use to make up the appropriate dose for each dose cohort. On each clinic day, the subject should return any unused study drug. A full accountability of these supplies by the site staff and the sponsor's designated Clinical Research

Associate (CRA) should be conducted before they are destroyed.

Cycles of MLN0128P and MLN0128PH are repeated every 4 weeks (28 days).

MLN0128 will be initially administered orally on a schedule consisting of daily administration of MLN0128 QDx3d QW on a 4-week cycle. On days when weekly paclitaxel is administered (Days 1, 8 [±1 day], and 15 [±1 day] of every 28-day cycle), MLN0128 will be administered in the clinic within 30 minutes of the completion of paclitaxel infusion. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 will be administered alone for subjects receiving MLN0128P and within 30 minutes of the completion of trastuzumab for subjects receiving MLN0128PH. The starting dose of MLN0128 is 6 mg daily for the first 3 days (Days 1-3) of each week. If a DLT is observed in 2 or more subjects in a cohort of 3 to 6 subjects treated with the starting dose of 6 mg, a new cohort of 3 to 6 subjects will be enrolled at either 4 mg or an intermediate dose level between 4 mg and 6 mg. With implementation of Amendment 1, alternate dosing schedules (such as QDx5d QW) of MLN0128 administration in combination with paclitaxel may be evaluated to optimize tolerability and exposure of the combination. For the intermittent dosing schedules (such as QDx3d QW or QDx5d QW), in subsequent dose escalation cohorts, MLN0128 will be administered at approximately 24 hours following completion of paclitaxel infusion. For example, on the QDx3d QW dose schedule, paclitaxel will be administered on Days 1, 8 [±1 day], and 15 [±1 day] and MLN0128 will be administered on Days 2-4, 9-11, 16-18, and 22-24 of every 4-week cycle. Likewise, on the QDx5d QW dose schedule, paclitaxel will be administered on Days 1, 8 [±1 day], and 15 [±1 day] and MLN0128 will be administered on Days 2-6, 9-13, 16-20, and 22-26 of every 4-week cycle.

Dose escalation will be according to a modified Fibonacci schema. For example, a starting dose of 6 mg may be escalated in successive cohorts to 8 mg, 10 mg, etc. or an intermediate dose between 2 planned doses may be evaluated. The level of dose escalation or a decision to go to an intermediate dose or a lower dose will be determined after discussion between the participating investigators and Millennium's medical monitor before dose escalation, but will not exceed the planned next escalated dose according to the modified Fibonacci schema.

Paclitaxel 80 mg/m^2 will be given intravenously (IV) weekly on Days 1, 8 (±1 day), and 15 (±1 day) of every 28-day cycle in combination with MLN0128. Paclitaxel will be administered according to the FDA label (Taxol® package insert) and institution's standard clinical practice.

HER2+ cancer subjects enrolled in Arm B of the expansion cohort will receive MLN0128P at the MTD^{MLN0128P} in addition to weekly trastuzumab (MLN0128PH). A 4 mg/kg loading dose of trastuzumab will be given intravenously on Cycle 1 Day 1, followed by 2 mg/kg IV weekly thereafter. For subjects entering expansion Arm B already receiving trastuzumab, the C1D1 dose will be 2 mg/kg if the last trastuzumab dose had been administered within 28 days. If the last trastuzumab dose was administered >28 days before C1D1, then the 4 mg/kg loading dose will be administered.

Trastuzumab will be administered intravenously on Days 1, 8 (±1 day), 15 (±1 day), and 22 (±1 day) of every 28-day cycle prior to paclitaxel administration on Days 1, 8 (±1 day), and 15 (±1 day) and prior to MLN0128 administration on Day 22 (± 1day) according to the FDA label (Herceptin® package insert) and institution's standard clinical practice.

DURATION OF TREATMENT:

In the absence of unacceptable treatment-related toxicity or disease progression, subjects may receive the combination treatment MLN0128P or MLN0128PH (expansion phase in Arm B only) treatment for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor. Subjects will remain on study as long as they continue to receive MLN0128, paclitaxel, or trastuzumab without additional anti-cancer therapies.

REFERENCE THERAPY(IES), DOSE, ROUTE AND REGIMEN:

None.

CRITERIA FOR EVALUATION:

Safety:

Safety will be assessed by periodic physical examinations, 12-lead electrocardiograms (ECGs), echocardiogram/multi-gated acquisition scan (MUGA), clinical laboratory assessments, in-home monitoring of glucose levels with a glucometer and monitoring of adverse events (AEs). Adverse events will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Site teleconferences between the sponsor and all participating sites will be held approximately every 1 to 2 weeks during the dose escalation phase to discuss any suspected AEs/DLTs that have occurred in subjects within each cohort. Participating Investigators and the Sponsor's Medical Monitor will review study drug-related toxicities from the current cohort during the site teleconferences before escalating to the next dose.

Pharmacokinetics:

The PK profile will be assessed by determining the plasma levels of MLN0128 and paclitaxel at intervals throughout the study. For subjects enrolled prior to Amendment 1, blood samples for PK profile will only be collected in subjects during the dose escalation phase at the following time points:

1. Cycle 1 Day 1 (C1D1): predose
2. Cycle 1, Day 1 (C1D1): immediately at the end of paclitaxel infusion (EOPI and pre-MLN0128 dose), and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-MLN0128 C1D1 dose, and
3. Cycle 1, Day 2 (C1D2 = 24 ±2 hours post-MLN0128 C1D1 dose): pre-MLN0128 dose, and
4. Cycle 2 Day 1 (C2D1): predose
5. Cycle 2, Day 1 (C2D1): immediately at EOPI and pre-MLN0128 dose, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-MLN0128 C2D1 dose.

For subjects enrolled following implementation of Amendment 1, blood samples for PK profile will only be collected during the dose escalation phase at the following time points:

1. Cycle 1 Day 1 (C1D1): predose
2. C1D1: immediately at EOPI, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-paclitaxel C1D1 dose, and
3. Cycle 1, Day 2 (C1D2 = 24 ±2 hours post-paclitaxel C1D1 dose): pre-MLN0128 dose, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-MLN0128 C1D2 dose, and
4. Cycle 2 Day 1 (C2D1): predose
5. C2D1: immediately at EOPI, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-paclitaxel C2D1 dose, and
6. Cycle 2, Day 2 (C2D2 = 24 ±2 hours post-paclitaxel C2D1 dose): pre-MLN0128 dose, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-MLN0128 C2D2 dose.

Pharmacodynamics:

Pharmacodynamic assessment will be made by evaluation of various biomarker levels in tumor biopsy samples pre- and post-treatment during both the dose escalation and expansion phases of the study.

CCI

[redacted]

Predictive Markers of Activity:

CCI

[redacted]

Efficacy:

Radiographic and/or physical assessments of the malignancy will be made at Screening/Baseline (within 28 days prior to the first study drug administration) and every 2 cycles (±7 days) thereafter. Objective response (complete response [CR] and partial response [PR]) as determined by the subject's best tumor response, duration of response, and time to progression will be assessed using Response Evaluation Criteria in Solid Tumors Criteria (RECIST) version 1.1. A confirmatory CT/MRI scan should be performed at approximately 4 weeks from the previous scan for all patients with an objective response of ≥ PR.

STATISTICAL METHODS:

Safety Analyses:

Safety data analysis will be conducted on all subjects receiving at least 1 dose of MLN0128. Analyses will consist of data summaries for clinical and laboratory parameters, and for AEs. The safety data from the dose escalation will be summarized by dose cohort; and by disease cohort (ie, Arms A and B) during the expansion phase. The number and percentage of subjects experiencing 1 or more AEs will be summarized by the relationship to study drug and severity. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Laboratory parameters will be summarized using descriptive statistics, by post-dosing shifts relative to baseline, and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized by changes from baseline values using descriptive statistics.

Efficacy Analyses:

Efficacy analyses will be conducted for subjects with measurable disease at study entry as defined by RECIST (version 1.1) with adequate baseline and post-baseline disease assessments. The efficacy results will be presented by individual subject and dose cohort, and by tumor histology. The number and percentage of subjects experiencing objective response (complete response and partial response) will be summarized. The duration of objective response will be summarized descriptively using the Kaplan-Meier method.

Pharmacokinetic Analyses:

PK parameters, including area under the curve **(**AUC), maximum concentration (C_{max}), minimum concentration (C_{min}), time of maximum concentration (T_{max}), and half life ($t_{1/2}$) for MLN0128 and paclitaxel will be determined. The additional intravenous PK parameters, clearance (CL), and volume of distribution (V_{ss}) will be estimated for paclitaxel. Comparisons across dose levels will be made to assess proportionality. In addition, comparison between single dose and multi-dose PK parameters will be made for assessment of steady-state drug accumulation.

2.1 Schedule of Events

Table 2.1 Schedule of Events – Cycle 1

Assessments	Screening /Baseline		Treatment						Termination Visit[20]
	Within 28 days	Within 14 days	Day 1 (prior to dose)	Day 1	Day 2[21]	Day 8 (±1 day)	Day 15 (± 1 day)	Day 22 (± 1 day)	
Informed Consent and HIPAA	X								
Medical History	X								
Vital signs, Height[1], Weight and ECOG PS		X[1]	X[22]			X	X	X	X
Complete Physical Examination[2]		X	X[22]			X	X	X	X
12-lead ECG[3]		X	X[22]	X[23]	X[23]	X	X	X	X
ECHO/MUGA	X								X
Hematology[4]		X	X			X	X	X	X
Chemistry[5]		X	X			X	X	X	X
Coagulation (PT/INR, PTT)		X					X		X
Fasting Serum Glucose[6]		X	X[22]		X[6]	X	X	X	X
Glycosylated Hemoglobin (HbA1c)		X							X
Fasting Lipid Profile[7]		X							X
Urinalysis[8]		X	X[22]			X	X	X	X
Serum or Urine Pregnancy Test[9]		X	X[22]						
PK Timing[10]			X	X	X				
Tumor Biopsies for PD Evaluation[11]		X	X			X	X		
Archival Tumor Tissue[12]		X							
Radiographic Tumor Evaluation and Tumor Markers[13]	X								X[24]
In-Home Daily Fasting Glucose Monitoring[14]					X	X	X	X	
AE Monitoring[15]			X	X	X	X	X	X	X
Concomitant Medications[16]	X	X	X	X	X	X	X	X	X
MLN0128 Treatment[17]				X[17]	X[17]	X[17]	X[17]	X[17]	
Paclitaxel Administration[18]			X			X	X		
Trastuzumab Administration[19] – Only in Arm B of Expansion Phase			X			X	X	X	

1. Height is only needed at Screening/Baseline.
2. Complete physical examination will be performed at Screening/Baseline, C1D1 and at the Termination visit. Symptom directed physical examination will be done on C1D8 (±1 day), C1D15 (±1 day) and C1D22 (±1 day).
3. All scheduled ECGs should be performed after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of ECG assessments coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.
4. Complete blood count (CBC) includes white blood cell count (WBC) with differential, hemoglobin (Hgb), hematocrit (Hct), and platelet count. CBC results performed pre-dose on Days 1, 8, 15 and 22 of Cycle 1 must be available and reviewed by the investigator prior to trastuzumab, paclitaxel, or MLN0128 dosing.
5. Full chemistry panel includes Chem 7 (sodium [Na], potassium [K] chloride [Cl], bicarbonate [CO_2], blood urea nitrogen [BUN], creatinine [Cr], glucose), liver function tests (LFTs - ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), lactate dehydrogenase (LDH), total protein, calcium, phosphate, and magnesium. Chem 7 and LFT results performed pre-dose on Days 1, 8, 15, and 22 of Cycle 1 must be available and reviewed by the investigator prior to trastuzumab, paclitaxel, or MLN0128 dosing. Electrolyte levels should be corrected as needed before MLN0128 dosing, or before paclitaxel or trastuzumab dosing on days when paclitaxel or trastuzumab are administered 24 hours before MLN0128 dosing.
6. Fasting serum glucose will be measured prior to dexamethasone premedication for subjects receiving MLN0128P or prior to trastuzumab infusion for subjects receiving MLN0128PH on Cycle 1 Day 1 (C1D1), pre-MLN0128 dose on C1D2 when the pre-MLN0128 dose PK sample is drawn (dose escalation phase only), and before dexamethasone premedication (prior to MLN0128 on C1D22 when paclitaxel is not administered) for subjects receiving MLN0128P or prior to trastuzumab infusion for subjects receiving MLN0128PH on C1D8 (±1 day), C1D15 (±1 day), C1D22 (±1 day) and at the Termination visit. Additionally, upon implementation of Amendment 1 and under Amendment 2, fasting blood glucose will be measured at 1 hour post-MLN0128 dosing on C1D2 when PK samples are drawn in the dose escalation phase only.
7. Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides.
8. Urinalysis will include macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (levels should be recorded if available) and microscopic analysis should be performed if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine, and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
9. Only for female subjects with child-bearing potential. Serum pregnancy test will be done at Screening/Baseline. Either serum or urine pregnancy test will be done on C1D1.
10. Plasma PK samples will be obtained for subjects in the dose escalation phase prior to determination of the MLN0128P MTD at the following time points under the original protocol: pre-dose, immediately at the end of paclitaxel infusion (EOPI and pre-MLN0128 dose), and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), 6 hours (± 30 min), and 24 ±2 hours post-MLN0128 dose on C1D1. The PK sample draw on C1D2 (24 hours post-MLN0128 dosing) will be obtained before C1D2 MLN0128 dosing. Upon implementation of Amendment 1, plasma PK samples will be obtained for subjects in the dose escalation phase of the study at the following time points: on C1D1, pre-dose, immediately at EOPI, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (±30 min), 4 hours (±30 min), and 6 hours (±30 min) post-paclitaxel infusion completion; and on C1D2, pre-MLN0128 dose, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (±30 min), 4 hours (±30 min), and 6 hours (±30 min) post-MLN0128 C1D2 dose.
11. Fresh tumor tissue biopsies will be taken from subjects who have accessible tumor tissues based on the Investigator's judgment and who have signed the consent for tumor biopsy. Fresh tumor tissue collections should coincide with the collection of PK samples at 3 hours ± 1 hour post-MLN0128 dose.
12. Every effort should be made for all subjects who have available archival tumor tissues to collect either paraffin blocks or a minimum of 10 unstained slides of archival tumor tissue for assessment of predictive/prognostic markers. Archival tumor tissues can be collected after the subject begins study drug treatment, if extra time is needed to locate the specimens.
13. Baseline CT (with contrast)/MRI of chest, abdomen and pelvis and relevant tumor markers (eg, cancer antigen [CA]125, prostate-specific antigen [PSA], CA19-9, CA27.29, CA15.3, and carcinoembryonic antigen [CEA]) must be obtained within 4 weeks prior to the first dose. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of ≥ PR. The same method (CT with contrast or MRI) must be used throughout the study.

14. Subjects will be given a glucometer on C1D2 to monitor daily fasting whole blood glucose level at home and will be instructed to notify the study doctor when the fasting glucose is abnormal. The early detection and treatment of hyperglycemia has been key in managing this drug-related adverse event effectively in previous human studies with MLN0128. Each institution should decide an abnormal fasting glucose level (ie, ≥ 140 mg/dL) where the treatment and close monitoring of hyperglycemia might be required.
15. Adverse events will be collected after administration of the first dose of MLN0128, paclitaxel or trastuzumab through 30 days following the last dose of study drug.
16. Concomitant medications will be collected from 30 days prior to the first dose of study drug (MLN0128, paclitaxel or trastuzumab) until termination of the study.
17. Prior to Amendment 1, MLN0128 was initially to be given orally on a schedule consisting of daily administration of MLN0128 for 3 days on, 4 days off repeated each week (QDx3d QW of a 4-week cycle). On days when weekly paclitaxel is administered (Days 1, 8 [±1 day], and 15 [±1 day] of every 28-day cycle), MLN0128 was to be administered in the clinic to the subject within 30 minutes of the completion of paclitaxel infusion. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 was to be administered alone for subjects receiving MLN0128P and within 30 minutes of the completion of trastuzumab for subjects receiving MLN0128PH. The starting dose of MLN0128 is 6 mg daily for the first 3 days (Days 1-3) of each week. Upon implementation of Amendment 1 in subsequent dose escalation cohorts, for the intermittent dosing schedule evaluated, MLN0128 is administered at approximately 24 hours following paclitaxel infusion during Weeks 1-3. For example, in the QDx3d QW dosing schedule, MLN0128 will be administered on Days 2-4, 9-11, 16-18, and 22-24 of each 4-week cycle; and, in the QDx5d QW dosing schedule, MLN0128 will be administered on Days 2-6, 9-13, 16-20, and 22-26 of each 4-week cycle. Electrolyte levels should be corrected as needed prior to MLN0128 dosing on days when paclitaxel is not administered. On days that paclitaxel is administered (with or without trastuzumab), electrolyte levels should be corrected prior to paclitaxel or trastuzumab dosing.
18. Paclitaxel 80 mg/m^2 will be given intravenously weekly on Days 1, 8 (±1 day), and 15 (±1 day) of every 28-day cycle according to the FDA label and institution's standard clinical practice. Concomitant medications used prior to and during the administration of paclitaxel will be recorded on the appropriate CRF pages. Prior to Amendment 1, on days when paclitaxel was administered, MLN0128 was to be given orally in the clinic within 30 minutes of completion of the paclitaxel infusion; and upon implementation of Amendment 1, MLN0128 will be given orally at approximately 24 hours following paclitaxel infusion. If paclitaxel dosing is altered ±1 day, MLN0128 administration should also be altered accordingly. Electrolyte levels should be corrected as needed prior to paclitaxel dosing (see footnote 19 for days when trastuzumab is administered).
19. Once the MTD of MLN0128P (MTD^{MLN0128P}) is determined for the dosing schedules evaluated, Arm B of the expansion phase will enroll HER2+ cancer subjects. These subjects will receive weekly trastuzumab in combination with MLN0128P at the MTD^{MLN0128P} on Days 1, 8 (±1 day), 15 (±1 day) and 22 (±1 day) of every 28-day cycle. Trastuzumab 4 mg/kg loading dose will be given on C1D1, with subsequent weekly doses at 2 mg/kg thereafter. For subjects entering expansion Arm B already receiving trastuzumab, the C1D1 dose will be 2 mg/kg if the last trastuzumab dose had been administered within 28 days. If the last trastuzumab dose was administered >28 days before C1D1, then the 4 mg/kg loading dose will be administered. Trastuzumab will be administered intravenously prior to paclitaxel and according to the FDA label and institution's standard clinical practice. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 will be administered within 30 minutes of the completion of the trastuzumab infusion. Concomitant medications used prior to and during the administration of trastuzumab will be recorded on the appropriate CRF pages. Electrolyte levels should be corrected as needed prior to trastuzumab dosing when trastuzumab is administered before paclitaxel.
20. Termination visit will be done within 30 days of last dose of MLN0128 or paclitaxel or trastuzumab, whichever is discontinued last.
21. Upon implementation of Amendment 2 subjects in the expansion phase were not required to return to clinic on C1D2.
22. The assessment does not need to be repeated if it was done within 3 days prior to the first dose.
23. 12 lead ECG 4 hours (± 30 min) after MLN0128 dosing on Day 1 for subjects enrolled on the original protocol and 4 hours (± 30 min) post-dose on Day 2 for subjects enrolled following implementation of Amendment 1. Upon implementation of Amendment 2, ECG is only performed for subjects in the dose escalation phase on C1D2.
24. Tumor assessments will only be done on subjects who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks.

Table 2.2 Schedule of Events – Cycle 2 and Subsequent Cycles

Assessments	Treatment														Termination Visit[18]
	Cycle 2						Cycles 3 and 4				Cycles 5 and Onward				
	Day 1		Day 2[16]	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)[17]	
	Pre-dose	Day 1													
Vital Signs, Weight and ECOG PS	X			X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[1]	X[1]			X	X	X	X[1]	X	X	X	X[1]	X	X	X	X[1]
12-lead ECG[2]	X														X
Hematology[3]	X			X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[4]	X			X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (PT/INR, PTT)	X						X	X			X	X			X
Fasting Serum Glucose[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Glycosylated Hemoglobin (HbA1c)							X[19]				X[19]				X
Fasting Lipid Profile[6]	X						X				X				X
Urinalysis[7]	X			X	X	X	X		X	X	X				X
PK Timing[8]	X	X	X												
Radiographic Tumor Evaluation and Tumor Markers[9]							X				X				X[20]
In-Home Daily Fasting Glucose Monitoring[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MLN0128 Treatment[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Paclitaxel Administration[13]		X		X	X		X	X	X		X	X	X		
Trastuzumab Administration[14] – Only in Arm B of Expansion Phase		X		X	X	X	X	X	X	X	X	X	X	X	
ECHO/MUGA[15]						X[15]				X[15]				X[15]	

1. All subjects will undergo complete physical exams on Day 1 of every cycle and at the Termination visit. All subjects will undergo symptom directed physical exams on Days 8 (±1 day), 15 (±1 day), and 22 (±1 day) in Cycles 2, 3, and 4. All subjects will undergo symptom directed physical exams on Days 8 (±1 day) and 15 (±1 day), and, additionally for subjects receiving MLN128PH, on Day 22 (±1 day) in Cycles 5 and beyond.
2. All scheduled ECGs should be performed after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of ECG assessments coincides with a blood collection, the ECG should be obtained before the nominal time of the blood collection. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.
3. CBC including WBC with differential, Hgb, Hct, and platelet count. CBC results performed pre-dose on Days 1, 8, 15, and 22 of every cycle must be available and reviewed by the investigator prior to trastuzumab, paclitaxel, or MLN0128 dosing.
4. Full chemistry panel includes Chem 7 (sodium [Na], potassium [K], chloride [Cl], bicarbonate [CO_2], blood urea nitrogen [BUN], creatinine [Cr], glucose), liver function tests (LFTs - ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, calcium, phosphate, and magnesium. Chem 7 and LFT results performed pre-dose on Days 1, 8, 15, and 22 of every cycle must be available and reviewed by the investigator prior to trastuzumab, paclitaxel, or MLN0128 dosing. Electrolyte levels should be corrected as needed prior to MLN0128 dosing, or prior to paclitaxel or trastuzumab dosing on days when paclitaxel or trastuzumab are administered 24 hours before MLN0128 dosing.
5. Fasting serum glucose will be performed prior to dexamethasone premedication for subjects receiving MLN0128P or prior to trastuzumab infusion for subjects receiving MLN0128PH, and included in the Chem 7 panel on Days 1, 8, 15, and 22 of every cycle prior to dosing. Subjects are required to fast overnight (nothing to eat or drink by mouth except water after midnight or a minimum of 8 hours) for all of these measurements.
6. Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein (LDL-C), triglycerides.
7. Urinalysis will include macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (levels should be recorded if available) and microscopic analysis should be performed if an abnormality is noted. Microscopic urinalysis will also be performed along with 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
8. Plasma PK samples will be obtained for subjects in the dose escalation phase prior to determination of the MLN0128P MTD at the following time points prior to Amendment 1: pre-dose, immediately at the end of paclitaxel infusion (EOPI and pre-MLN0128 dose), and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-MLN0128 dose on C2D1. Upon implementation of Amendment 1, plasma PK samples will be obtained for subjects in the dose escalation phase of the study at the following time points: on C2D1, pre-dose, immediately at EOPI, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-paclitaxel infusion completion; and on C2D2, pre-MLN0128 dose, and at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min) post-MLN0128 C2D2 dose.
9. CT (with contrast)/MRI of chest, abdomen and pelvis and relevant tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA) will be obtained every 2 cycles (+ 7 days) starting at C3D1 for response assessment by RECIST version 1.1. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of ≥ PR. The same method (CT with contrast or MRI) must be used throughout the study.
10. Subjects will continue to monitor their daily fasting blood glucose levels at home with a glucometer and will be instructed to notify the study doctor when the fasting glucose is abnormal. The early detection and treatment of hyperglycemia has been key in managing this drug-related adverse event effectively in previous human studies with MLN0128. Each institution should decide an abnormal fasting glucose level (ie, ≥ 140 mg/dL) where the treatment and close monitoring of hyperglycemia might be required.
11. Concomitant medications will be collected from 30 days prior to the first dose of study drug (MLN0128, paclitaxel, or trastuzumab) until termination of the study.
12. Prior to Amendment 1, MLN0128 was to be given orally on an intermittent schedule consisting of daily administration of MLN0128 for 3 days on, 4 days off repeated each week (QDx3d QW of a 4-week cycle). On days when weekly paclitaxel is administered (Days 1, 8 [±1 day], and 15[±1 day] of every 28-day cycle), MLN0128 was to be administered in the clinic to the subject within 30 minutes of the completion of paclitaxel infusion. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 was to be administered alone for subjects receiving MLN0128P and within 30 minutes of the completion of trastuzumab infusion for subjects receiving MLN0128PH. Upon implementation of Amendment 1 in subsequent dose escalation cohorts, for the intermittent dosing schedule evaluated, MLN0128 is administered at approximately 24 hours following paclitaxel infusion. For example, in the QDx3d QW dosing schedule, MLN0128 will be administered on Days 2-4, 9-11, 16-18, and 22-24 of each 4-week cycle; and, in the QDx5d QW dosing schedule, MLN0128 will be administered on Days 2-6, 9-13, 16-20, and 22-26 of each 4-week cycle. Electrolyte levels should be corrected as

needed prior to MLN0128 dosing on days when paclitaxel is not administered. On days that paclitaxel is administered (with or without trastuzumab) electrolyte levels should be corrected prior to paclitaxel or trastuzumab dosing.

13. Paclitaxel 80 mg/m^2 will be given intravenously weekly on Days 1, 8 (±1 day), and 15 (±1 day) of every 28-day cycle according to the FDA label and institution's standard clinical practice. Prior to Amendment 1, on days when paclitaxel was administered, MLN0128 was given orally in the clinic within 30 minutes of completion of the paclitaxel infusion; and upon implementation of Amendment 1, MLN0128 is given orally at approximately 24 hours following paclitaxel infusion. If paclitaxel dosing is altered ±1 day, MLN0128 administration should also be altered accordingly. Concomitant medications used prior to and during the administration of paclitaxel will be recorded on the appropriate CRF pages. Electrolyte levels should be corrected as needed prior to paclitaxel dosing (see footnote 14 for days when trastuzumab is administered).
14. Once the MTD of MLN0128P (MTDMLN0128P) is determined for the dosing schedules evaluated, Arm B of the expansion phase will enroll HER2+ cancer subjects. These subjects will receive weekly trastuzumab in combination with MLN0128P at the MTDMLN0128P on Days 1, 8 (±1 day), 15 (±1 day), and 22 (±1 day) of every 28-day cycle. Trastuzumab 2 mg/kg will be given weekly starting with C1D8 (±1 day). Trastuzumab will be administered intravenously prior to paclitaxel and according to the FDA label and institution's standard clinical practice. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 will be administered within 30 minutes of the completion of trastuzumab infusion. Concomitant medications used prior to and during the administration of trastuzumab will be recorded on the appropriate CRF pages. Electrolyte levels should be corrected as needed prior to trastuzumab dosing when trastuzumab is administered before paclitaxel.
15. ECHO/MUGA should be performed every 3 cycles in subjects receiving MLN0128PH, starting with C4D1, and at the Termination visit.
16. Upon implementation of Amendment 2, subjects in the expansion phase were not required to return to clinic on C2D2.
17. Day 22 (±1 day) clinic visit will be only required for subjects receiving MLN0128PH.
18. Termination visit will be within 30 days of last dose of MLN0128 or paclitaxel or trastuzumab, whichever is discontinued last.
19. HbA1c should be performed on Day 1 every 3 months starting with C4D1.
20. Tumor assessments will only be done on subjects who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
CCI	[redacted]
ALT	alanine aminotransferase
ASaT	all subjects as treated
ANC	Absolute Neutrophil Count
AST	aspartate aminotransferase
ATP	adenosine tri-phosphate
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hr
AUC_{0-last}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
CCI	[redacted]
BID	twice a day
CCI	[redacted]
BUN	blood urea nitrogen
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum steady-state plasma concentration
C_{min}	minimum plasma concentration
CA15.3	Cancer Antigen 15.3
CA19-9	Cancer Antigen 19-9
CA27.29	Cancer Antigen 27.29
CA125	Cancer Antigen 125
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CL	clearance
CNS	central nervous system
CR	Complete Response
CRA	Clinical Research Associate
CRF	case report form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report

CXDY	cycle x day y
DLT	Dose Limiting Toxicity
DPP-4	dipeptidyl peptidase 4
dUTP	deoxyuridine triphosphate
4EBP1	Eukaryotic Initiation Factor 4E-binding Protein 1
EC	Ethics Committee
ECG(s)	electrocardiogram(s)
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ER	estrogen receptor
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
FBG	fasting blood glucose
FDA	Food and Drug Administration
FBXW7	F-box and WD repeat domain containing 7
CCI [redacted]	[redacted]
FSG	fasting serum glucose
GCP	Good Clinical Practice
GI	gastrointestinal
CCI [redacted]	[redacted]
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HDL-C	High Density Lipoprotein Cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP(s)	Investigational Product(s)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous, intravenously
LDL-C	Low Density Lipoprotein

LFT	liver function test
LKB1	Liver Kinase B1
LVEF	Left Ventricular Ejection Fraction
MCL-1	Myeloid Leukemia Sequence 1
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc.
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mechanistic (formerly Mammalian) Target of Rapamycin
mTORC	mTOR complex
MUGA	Multiple Gated Acquisition Scan
Myc (N/C)	C-Myc, N-Myc oncogene
NCI	National Cancer Institute
CCI	[redacted]
NF1	Neurofibromin 1
NHL	Non-Hodgkin Lymphoma
NYHA	New York Heart Association
P53(TP53)	Protein 53 (tumor protein 53)
P85(PIK3R1)	Regulatory subunit p85 (Phosphoinositide 3-kinase, regulatory subunit 1)
PBC(s)	peripheral blood cell(s)
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PE	physical examination
PI	Principal Investigator
PIC	Patient Informed Consent
PI3K(s)	Phosphoinositol-3-Kinase(s)
PIK3CA	Phosphoinositide 3-kinase Alpha Catalytic Subunit
PK	pharmacokinetic(s)
PO	by mouth (oral)
PR	partial response
PRAS40	proline rich AKT substrate of 40 kDa
PSA	Prostate-specific Antigen
PT	Prothrombin Time
PTEN	Phosphatase and Tensin Homolog

PTT	Partial Thromboplastin Time
QD	once a day
QDx3d QW	once a day 3 on 4 days off repeated each week
QDx5d QW	once a day 5 days on 2 days off repeated each week
QT	interval on ECG between the start of the Q wave and end of the T wave
QTc	QT interval corrected for heart rate
QW	once weekly
Rapalog	rapamycin analog
RECIST	Response Evaluation Criteria in Solid Tumors
S6	ribosomal protein S6
S6K	ribosomal S6 kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
$t_{1/2}$	plasma half-life
T_{max}	time of maximum plasma concentration
TORC	target of Rapamycin Complex
TSC1/2	tuberous sclerosis complex 1/2
ULN	Upper Limit of Normal
US	United States
WBC	white blood cell

Definition of Terms:

Investigational Product (IP) or Study Drug:

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use." (from E6 International Conference on Harmonisation [ICH] 1.33)

The terms "IP" and "study drug" may be used interchangeably in the protocol.

5 INTRODUCTION

MLN0128 (formerly INK128) is a potent and highly selective, Adenosine Tri-Phosphate (ATP)-competitive inhibitor of the serine/threonine kinase termed as the mammalian target of rapamycin (mTOR). MLN0128 is mechanistically distinct from the allosteric inhibitors of mTOR (rapamycin and its derivatives, referred to as rapalogs). The rapalogs inhibit mTOR complex 1 only; this is distinct from MLN0128 that inhibits both mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). MLN0128 is formulated as capsules intended for the treatment of solid and hematologic malignancies.

A comprehensive review of MLN0128 is contained in the Investigator's Brochure (IB) supplied by Millennium Pharmaceuticals, Inc. (Millennium). The investigator should review this document before initiating this study.

5.1 Clinical Experience with MLN0128

5.1.1 Clinical Safety

The safety and tolerability of single-agent MLN0128 administration is being studied in this first-in-human (FIH), phase 1, dose-finding study in subjects with advanced solid malignancies and a second phase 1 study (Study INK128-002) in subjects with multiple myeloma and non-Hodgkin lymphoma, including Waldenström Macroglobulinemia. A third phase 1b trial (Study INK128-003) is evaluating MLN0128 in combination with paclitaxel in subjects with advanced solid malignancies.

Repeated in 28-day cycles, the dosing regimens (and dose ranges) studied to date in INK128-001 are the following: once daily (QD; 2-7 mg), once weekly (QW; 10-40 mg), once daily for 3 consecutive days per week (QD×3d QW; 6-20 mg), and once daily for 5 consecutive days per week (QD×5d QW; 7-13 mg). As of 09 December 2012, dose-limiting toxicities have included hyperglycemia, asthenia, fatigue, mucositis, and rash. SAEs attributed to MLN0128 have included hyperglycemia, asthenia, mucosal inflammation, stomatitis, esophagitis, nausea, anemia, renal failure, cardiac arrest, and ventricular fibrillation.

There have been 5 deaths during the study attributable to (1 subject each) pleural effusion, small intestinal obstruction, cancer pain, disease progression, and cardiac arrest. The only death considered related to study drug was due to cardiac arrest in a subject receiving 6 mg QD.

Regardless of causality, adverse events (AEs) with intensity Grade ≥ 3 have been reported in ≤ 10% of subjects and include hyperglycemia, asthenia, mucosal inflammation, anemia, lymphopenia, hypophosphatemia, and rash. Inclusive of all grades, the most frequently reported AEs (those with ≥ 20% incidence) include hyperglycemia, asthenia, fatigue, mucosal inflammation, decreased appetite, nausea, vomiting, diarrhea, rash, and pruritus.

As of 09 December 2012, there have been 2 dosing regimens studied in INK128-002. In repeated 28-day cycles, they are QD (2-7 mg) and QD×3d QW (9-12 mg). DLTs have included asthenia, fatigue, mucosal inflammation, rash, urticaria, and thrombocytopenia. None of the13 SAEs reported was attributed to MLN0128. Two subjects have died during the study of events not related to MLN0128: 1 death was due to subdural bleeding, and the other death was due to an unspecified cause. Regardless of causality, AEs with intensity Grade ≥ 3 reported in at least 2 subjects include fatigue, mucosal inflammation, neutropenia, thrombocytopenia, hypocalcemia, hypophosphatemia, and pneumonia. Inclusive of all grades, the most frequently reported AEs (those with ≥ 20% incidence) include hyperglycemia, fatigue, stomatitis, decreased appetite, nausea, vomiting, diarrhea, anemia, and thrombocytopenia.

As of 09 December 2012, the MLN0128 dosing regimens (and dose ranges) studied in INK128-003 are QD×3d QW (6-10 mg), QD×5d QW (7 mg), and QW (30 and 40 mg). MLN0128 is administered in combination with paclitaxel (80 mg/m^2) administered on Days 1, 8, and 15 of each 28-day cycle. The dose escalation phase of this study has completed and the administration of MLN0128 plus paclitaxel with or without trastuzumab is being evaluated in the expansion phase. Observed DLTs include fatigue, mucosal inflammation, rash, nausea, diarrhea, leukopenia, neutropenia, and thrombocytopenia. SAEs observed with the MLN0128 + paclitaxel are dehydration, diarrhea, vomiting, and mucositis. There have been 7 deaths during the study including 4 due to disease progression, and 1 death each due to myocardial infarction, enlarging tumor mass causing tracheal compression, and pneumonia. None of these deaths were attributed to MLN0128 or paclitaxel. Regardless of causality, AEs with intensity Grade ≥ 3 reported in at least 2 subjects are hyperglycemia, fatigue, diarrhea, dehydration, neutropenia, and hypophosphatemia. Inclusive of all grades, the most frequently reported AEs (those with ≥ 20% incidence) include hyperglycemia, asthenia, fatigue, mucosal inflammation, anorexia, rash, nausea, vomiting, diarrhea, dehydration, hypokalemia, hypophosphatemia, anemia, neutropenia, urinary tract infection, and constipation.

Details on these studies are provided in the MLN0128 IB.

5.1.2 Clinical Pharmacokinetics

MLN0128 displays high oral bioavailability and predicable PK with minimal levels of steady state accumulation. It is rapidly absorbed with T_{max} occurring between 1 to 4 hours following oral administration. The mean elimination half-life of MLN0128 ranged from approximately 7 to 11 hours across 4 dose levels. The mean accumulation index of MLN0128 following multiple doses ranged from 0.7-fold to 1.7-fold. The mean steady-state plasma concentrations ($C_{max,ss}$) ranged from 52 to 232 nM. Comparisons of plasma exposures (C_{max} and area under the plasma concentration-time curve from 0 to 24 hr [AUC_{0-24}]) following oral doses of MLN0128 suggest dose-linear plasma pharmacokinetics.

5.2 Study Rationale

The mTOR is a kinase that regulates cell growth, translational control, angiogenesis and cell survival by integrating nutrient and hormonal signals. mTOR plays a key role in several pathways that are frequently dysregulated in human cancer.[1] The mTOR activity in the intracellular signaling complexes (mTORC1 and mTORC2) is an important therapeutic target because (i) it is a key intracellular point of convergence for a number of cellular signaling pathways; (ii) it appears to be a stable target that does not mutate; (iii) inhibiting mTOR may inhibit abnormal cell proliferation, tumor angiogenesis and abnormal cellular metabolism. Thus, mTOR inhibitors may be effective as single agents and may enhance the efficacy of other cancer treatments.

mTOR operates in 2 distinct multi-protein complexes, mTORC1 and mTORC2. mTORC1, stimulated by growth factors and amino acids, regulates cell growth by controlling the activity of the ribosomal protein S6 (S6) kinases and eukaryotic initiation factor 4E-binding Protein (4EBP) proteins.[2] Rapamycin (Rapamune®) is an mTORC1 inhibitor that has been approved for prophylaxis of organ rejection in subjects receiving renal transplants. Although rapamycin has been shown to possess some antitumor activity, its poor aqueous solubility and chemical stability has precluded its utilization at doses necessary for anticancer treatment. This led to development of new analogues of rapamycin (rapalogs). Those currently in clinical development as anticancer agents include temsirolimus (cell cycle inhibitor-779 or CCI-779), everolimus (RAD-001), and deforolimus (AP23573). These agents have demonstrated antiproliferative activity against a range of malignancies in preclinical studies and clinical evaluations have revealed some encouraging data in selected disease populations. In 2007, temsirolimus was approved by the US Food and Drug Administration (FDA) for treatment of advanced renal cell cancer and in March 2009, everolimus was approved for treatment of advanced renal cancer after failure of treatment with sunitinib or sorafenib.[3, 4] Despite some encouraging clinical data, the rapalogs have limitations and efficacy may be confined to distinct subject subtypes or diseases. There are several scientific hypotheses that may explain the limited success of rapalogs. Inhibition of mTORC1 (without inhibition of mTORC2) leads to activation of AKT kinase due to a feedback mechanism, and this upregulation of AKT may actually accelerate tumor progression, thus limiting the clinical efficacy of rapalogs.[5]

Additionally, mTORC2 phosphorylates AKT which is required for full activity of AKT. Activated AKT is involved in cancer cell survival, proliferation, growth, metabolism, angiogenesis and metastasis. Inhibition of AKT activity through mTORC2 inhibition has been explored for anticancer therapeutics and preclinical investigations have shown inhibition of mTORC2 blocks cancer growth.[6] mTORC2 inhibition can also reverse the feedback activation of AKT induced by mTORC1 inhibition. Therefore, mTOR inhibitors that target both mTOR complexes such as MLN0128 may achieve greater clinical efficacy than rapalogs.[7]

Combination of MLN0128 with paclitaxel inhibited tumor cell proliferation more effectively than either of the single agent in preclinical experimental models. In most instances, MLN0128/paclitaxel combination led to an increase in cell cycle arrest and apoptosis. In vivo, MLN0128/paclitaxel combination in xenograft models of endometrial and breast cancers displayed enhanced anti-tumor efficacy and blockade of TORC1/2 signaling in a dose dependent manner. Tumor re-growth upon stop of drug treatment was further delayed by the combination as compared to treatment with either of the single agents. The combination of MLN0128 and paclitaxel was well tolerated in mouse xenograft tumor models (unpublished data from Intellikine labs).

To date, this study (INK128-003) has evaluated MLN0128 administration in combination with paclitaxel on a QDx3d QW dosing schedule in subjects with advanced solid malignancies. Amendment 1 will evaluate additional dosing schedules for MLN0128 administration in combination with paclitaxel (such as QDx5d QW dosing) to maximize tolerability and exposure of the doublet combination and further defines the expansion cohort patient population beyond HER2+ breast cancer. Recent preclinical in vivo xenograft data also suggest that administration of MLN0128 approximately 24 hours, instead of within 30 minutes, following paclitaxel infusion may provide more synergy in tumor cell kill; therefore, for subsequent cohorts opened following Amendment 1, MLN0128 will be administered approximately 24 hours following paclitaxel administration.

5.3 Summary of Overall Risks and Benefits

Currently, 206 subjects have participated in phase 1 studies including 145 subjects in single-agent studies INK128-001 and INK128-002 (N = 106 and N = 39, respectively); and 61 subjects in the paclitaxel combination study INK128-003. Toxicities have been mostly Grades 1 and 2, reversible, and manageable with supportive care and/or interruption or dose reduction of study drug. Commonly reported study drug-related AEs have included hyperglycemia, asthenia, fatigue, mucosal inflammation, decreased appetite, rash, nausea, vomiting, and diarrhea. This emerging safety profile is consistent with those of other TORC1/2 and PI3K pathway inhibitors.

As of 2012, there are no FDA-approved TORC1/2 inhibitors. Rapamycin and rapalogs are TORC1 inhibitors with well-described toxicity profiles. Common toxicities include the following: immunosuppression with the potential to increase the risk of both nonserious and serious infections, and/or malignancies; mucositis, stomatitis, and mouth sores with a frequency from 41% to 78%; anorexia (approximately 30%), pneumonitis including interstitial lung disease (5%-36%); diarrhea (25%-56%); skin toxicity (48%-66%) which manifests typically as maculopapular or acneform rash, skin dryness, eczema, skin discoloration, and nail dystrophy; hyperlipidemia (hypercholesteremia and/or hypertriglyceridemia) with incidences from 8% to

44%; hyperglycemia (8%-22%); thrombocytopenia (10%-33%); anemia (27%-94%); leucopenia (27%-38%); hypokalemia (11%-21%); hypophosphatemia (15%-49%); hypertension (4%-7% in renal cancer subjects); elevated serum creatinine (37%-57%); elevated liver function tests (approximately 20%); arthralgia (25%-30%); asthenia (about 30%); and peripheral edema (24%-35%).[3, 4, 8, 9] Serious infections have included sepsis, opportunistic infections, and even death. An increase in the development of lymphomas is also a possibility because of the immunosuppression. Additionally, hypersensitivity reactions (18%), and fatal bowel perforation (1%) have been reported. Rapidly progressive, and sometimes fatal, acute renal failure not clearly related to renal cancer disease progression, abnormal wound healing, and increased risk of developing intracerebral bleeding (including fatal outcomes) in subjects with central nervous system (CNS) malignancies and/or receiving anticoagulation therapy have been reported in subjects receiving temsirolimus. Because of potential hazard to the developing fetus, women of childbearing potential are advised to avoid becoming pregnant while receiving rapamycin or rapalogs.[3, 4, 9]

The toxicities of rapamycin or rapalogs are typically reversible and infrequently serious. MLN0128 targets both TORC1 and TORC2, and thus may prove to have a different risk/benefit profile from the rapalogs. There is no human information available on inhibition of TORC2 alone. The safety profile of MLN0128 continues to be explored in advanced malignancies, including non-Hodgkin lymphoma (NHL), and hematologic malignancies.

Paclitaxel is an antimicrotubule agent approved by the FDA and EMA for treatment of breast, ovarian, and non-small cell lung cancers. Common side effects (≥ 10%) observed with paclitaxel include: neutropenia or leucopenia, thrombocytopenia, anemia, infections, bleeding, red cell transfusions, peripheral neuropathy, hypersensitivity reaction, myalgia/arthralgia, hypotension, abnormal electrocardiograms (ECGs), nausea and vomiting, mucositis, alopecia, ALT (SGOP) elevation, elevated alkaline phosphatase, and injection site reaction.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred despite premedication. All subjects should be pretreated according to the package insert Taxol® package insert.[10]

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2) and is approved by the FDA and EMA for the treatment of breast and gastric cancer with HER2 overexpression. The most common serious adverse reactions (≥ 5%) associated with trastuzumab infusion (Herceptin®) include pain, asthenia, fever, chills, headache, abdominal pain, back pain, infection, flu symptom, accident injury, allergic reaction, tachycardia, congestive heart failure (7% as a single agent and 28% in combination with anthracycline and

cyclophosphamide), nausea, diarrhea, vomiting, peripheral edema and edema, bone pain, arthralgia, insomnia, dizziness, parenthesis, depression, increased cough, dyspnea, rhinitis, pharyngitis, sinusitis, and rash.[11]

Based on the limited safety data from Study INK128-001 thus far, it does not appear that MLN0128 has overlapping toxicities of neutropenia, peripheral neuropathy or cardiomyopathy which frequently limit paclitaxel and/or trastuzumab administration.

6 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 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
- [redacted]

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

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]) 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 ($MTD^{MLN0128P}$) ± 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)

7.2 Dose Escalation Phase

The dose-escalation phase of the study is to determine the MTD and the DLT of MLN0128 when given orally on Days 1-3 each week of a 4-week cycle (QDx3d QW) or via alternate dosing schedules (such as QDx5d QW) in combination with paclitaxel on Days 1, 8, and 15 of each cycle (MLN0128P) in subjects with advanced solid malignancies. A cycle is defined as 4 weeks.

7.2.1 Dose Limiting Toxicity

Adverse events will be graded according to the NCI-CTCAE v4.0. A copy of this grading scale will be provided to the study sites upon request or can be accessed at http://ctep.cancer.gov/forms/CTCAEv4.pdf.

Dose-limiting toxicity is defined as either of the following occurring during Cycle 1 (Days 1 - 28) and attributable to MLN0128P as shown in Table 7.1.

Table 7.1 Definition of Dose-Limiting Toxicity

• Grade ≥ 3 non-hematologic toxicity, **except for** o Alopecia; o Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all subjects should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment); o Grade 3 hyperglycemia lasting ≤ 14 days (all subjects should receive optimal antihyperglycemic treatment) o Grade 3 rash lasting ≤ 3 days (all subjects should receive topical steroid treatment, oral antihistamines, and pulse oral steroids, if necessary)
• Grade 3 thrombocytopenia with hemorrhage
• Grade 4 neutropenia lasting > 7 days in the absence of growth factor support
• Grade 4 neutropenia of any duration associated with fever ≥ 38.5°C and/or infection
• Any other Grade 4 hematologic toxicity
• Inability to administer at least 75% of doses of MLN0128 within Cycle 1 due to drug-related toxicity
• Any clinically significant occurrence which the Investigators and Sponsor agree would place subjects at undue safety risk

Subjects who experience an AE that meets the definition for a DLT during or after completing Cycle 1 should have their study drug treatment interrupted. If the event resolves to Grade ≤ 1 or baseline values within 28 days of interrupting planned therapy, and in the opinion of the investigator and the Sponsor's Medical Monitor, the benefits of continuing treatment outweigh the risks posed by the toxicity, subjects may continue study treatment with paclitaxel (at the same dose or at a 25% dose reduction) and MLN0128 (at a dose based on the AE and guidance provided in Table 7.3) with approval of the Sponsor's Medical Monitor. Subjects receiving MLN0128 at a starting dose of 6 mg will have MLN0128 dose- reduced to ≥ 4 mg if dose reduction is required.

The Sponsor's Medical Monitor should be contacted prior to any dose modification in paclitaxel or MLN0128 for any subject in the study.

7.2.2 Maximum Tolerated Dose

The MTD of MLN0128P ($MTD^{MLN0128P}$) is defined as the highest dose level of MLN0128 when given orally for each dosing schedule evaluated (ie, QDx3d QW or QDx5d QW each week) of a 4-week cycle in combination with paclitaxel (80 mg/m^2) on Days 1, 8, and 15 of each cycle at which no more than 1 out of 6 subjects experiences a DLT during the first cycle (28 days) of therapy.

7.2.3 Dose Escalation Plan to Determine the Maximum Tolerated Dose

Cohorts of 3 to 6 subjects with advanced solid malignancies will be enrolled at each MLN0128 dose level evaluated in combination with paclitaxel in 4-week cycles. Subjects at each dose level will be treated and observed for DLT through the end of the first cycle. Each subject will participate in only 1 cohort and 1 dosing schedule.

The starting dose of MLN0128 is 6 mg daily for the first 3 days (Days 1-3) of each week. Dose escalation will only proceed if no DLT is observed in a cohort of 3 subjects. If a DLT is observed in only 1 subject in a cohort of 3 subjects, an additional 3 subjects may be enrolled up to a total of 6 subjects at this dose level. Dose escalation will then only proceed if no more than 1 subject in the cohort of 6 subjects has experienced a DLT during the first cycle of treatment. If a DLT is observed in 2 or more subjects in a cohort of 3 or 6 subjects, an additional 3 subjects will be enrolled for a total of 6 subjects at the previous lower dose level, if only 3 subjects were treated at that lower dose level. If a DLT is observed in 2 or more subjects in a cohort of 3 to 6 subjects treated with the starting dose of 6 mg, a new cohort of 3-to 6 subjects will be enrolled at either 4 mg or an intermediate dose level between 4 mg and 6 mg. Table 7.2 below provides a summary of the dose escalation decision rules for determination of the MTD.

Table 7.2 Maximum Tolerated Dose Determination and Cohort Expansion

Number of Subjects per Cohort With a DLT During the Cycle 1 (Days 1 to 21)	Dose Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter up to 3 more subjects at this dose level. If none of the 3 additional subjects has a DLT, proceed to the next dose level. If 1 or more of the 3 additional subjects has a DLT, then dose escalation will be stopped, and the MTD will have been exceeded. Up to 3 additional subjects may be entered at a lower dose level if only 3 subjects were treated previously at that dose or a new cohort of 3 subjects at an intermediate dose level may be evaluated.
≥ 2	Dose escalation will be stopped, and the MTD will have been exceeded. Up to 3 additional subjects will be entered at a lower dose level if only 3 subjects were treated previously at that dose or a new cohort of 3 subjects at an intermediate dose level may be evaluated.
≤ 1 out of 6 at the highest dose evaluated.	This is generally the MTD.

Abbreviations: DLT = dose limiting toxicity; MTD = maximum tolerated dose.

All participating sites are required to send in DLT notification forms within 24 hours of learning of the event (details will be provided in Study Reference Manual). Dose-limiting toxicities will immediately be communicated to all participating sites via emails and/or conference calls. Additionally, site teleconferences between the Sponsor and all participating sites will be held approximately every 1 to 2 weeks during the dose escalation phase to discuss any suspected AEs/DLTs that have occurred in subjects within each cohort. Participating Investigators and the Sponsor's Medical Monitor will review study drug-related toxicities from the current cohort during the site teleconferences before escalating to the next dose level or starting a lower dose.

7.2.4 Expansion Phase

After the $MTD^{MLN0128P}$ has been identified, 2 arms of subjects will be enrolled in parallel. Approximately 30 subjects may be enrolled in the expansion phase of the study:

- Arm A will consist of approximately 12 to 15 safety-evaluable HER2- cancer subjects receiving MLN0128P at the $MTD^{MLN0128P}$. Additional subjects may be enrolled into lower dose cohorts of MLN0128P of Arm A.
- Arm B will consist of approximately 12 to 15 safety-evaluable HER2+ cancer subjects receiving MLN0128P at the $MTD^{MLN0128P}$ plus weekly trastuzumab (MLN0128PH). Up to 3 subjects will be enrolled initially in Arm B and observed for one cycle prior to enrolling additional subjects into this arm. Additional subjects may be enrolled into lower dose cohorts of MLN0128P + trastuzumab of Arm B.

It is estimated that in total up to 75 subjects may be enrolled in the study.

7.2.5 Intra-Subject Dose Escalation

Once the $MTD^{MLN0128P}$ is determined, intra-subject dose escalation is only allowed (at the Investigator's discretion and with the Sponsor's approval) in subjects actively receiving MLN0128P at a dose lower than the $MTD^{MLN0128P}$ for a minimum of 8 weeks in the absence of disease progression or unacceptable treatment-related toxicity.

7.2.6 Dose Modification or Treatment Delay for Toxicity

7.2.6.1 Dose Modification for Paclitaxel and MLN0128-Related Toxicities

The Investigator should try to the best of his/her ability to assess whether an adverse event is possibly related to study drug, and if so, attribute it to MLN0128 only, paclitaxel only, or MLN0128 and paclitaxel, and treat the subject accordingly. This section and Table 7.3 below provides suggested guidelines for the management of various study drug-related toxicities in subjects receiving paclitaxel and MLN0128.

Paclitaxel dosing should be withheld for ≥ Grade 2 paclitaxel-related toxicities and resumed at the same dose or at a 25% dose reduction, which refers to a decrease of 20 mg/m^2 depending on the timing of recovery and number of episodes occurred (see Table 7.3 and Table 7.4). If paclitaxel dosing is delayed due to paclitaxel-related toxicities for > 2 consecutive planned treatment weeks despite supportive treatment per standard clinical practice or more than 2 dose reductions of paclitaxel (≤ 40 mg/m^2) is required, stop paclitaxel therapy.

In general, MLN0128 dosing should be withheld for ≥ Grade 2 renal insufficiency or ≥ Grade 3 MLN0128-related non-hematologic toxicities.

Table 7.3 below provides suggested guidelines for the investigator to use along with his/her best judgment for MLN0128 and paclitaxel dose delay and/or reduction based on the AE observed. Subjects with a starting dose of 6 mg MLN0128 will have the dose reduced to ≥ 4 mg if dose reduction is required. If MLN0128 dosing is delayed due to MLN0128-related toxicities for > 28 consecutive days despite supportive treatment per standard clinical practice or more than 2 dose reductions of MLN0128 is required, stop MLN0128 and paclitaxel therapy, discontinue the subject from the study, and complete the follow-up visit within 30 days of the last administration of MLN0128 or paclitaxel, whichever is discontinued last.

The Sponsor's Medical Monitor should be contacted prior to any dose modification in paclitaxel and/or MLN0128 for any subject in the study.

Table 7.3 Guidelines for Paclitaxel and MLN0128 Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Absolute Neutrophil Count (ANC)		
Grade 2 < 1500 - 1000/mm^3	No change. Continue MLN0128 at same dose and schedule.	No change. Continue paclitaxel at same dose and schedule. For ANC ≤ 1500/mm^3 consider the use of prophylactic myeloid growth factors (ie, GCSF) • Start one or two days after paclitaxel infusion and use for 2–6 days according to subject's need, at physician discretion, and to avoid dose reduction. • Growth factor should not be given on the same day as paclitaxel infusion. • GCSF is preferred over peg-filgrastim due to the weekly dosing of paclitaxel in this study.

Grade 3 < 1000 – 500/mm^3	No change. Continue MLN0128 at same dose and schedule.
	
	Consider use of prophylactic myeloid growth factor support per guidelines above.
		Hold paclitaxel until ANC > 1000/mm^3
		
		Resume paclitaxel based on timing of recovery and number of previous episodes:
		• ≤ 2 weeks of interrupting planned therapy
		  ○ First episode—no change to paclitaxel dose
		  ○ ≥Second episode—reduce paclitaxel dose by 25% for all subsequent cycles
		• > 2 weeks of interrupting planned therapy—stop paclitaxel and discontinue subject from study

		Consider use of prophylactic myeloid growth factor support per guidelines above.

Grade 4 < 500/mm^3	Hold MLN0128 until ANC > 1000/mm^3
	
	Resume MLN0128 based on timing of recovery:
	• ≤ 1 week—no change to MLN0128 dose
	• > 1 but ≤ 2 weeks—reduce MLN0128 to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles
	• > 2 weeks—stop MLN0128 and discontinue subject from study
	
	Consider use of prophylactic myeloid growth factor support per guidelines above.
		Hold paclitaxel until ANC > 1000/mm^3
		
		Resume paclitaxel based on timing of recovery and number of previous episodes:
		• ≤ 2 weeks of interrupting planned therapy
		  ○ First episode—no change to paclitaxel dose
		  ○ ≥ Second episode—reduce paclitaxel dose by 25% for all subsequent cycles
		• > 2 weeks of interrupting planned therapy—stop paclitaxel and discontinue subject from study
		
		Consider use of prophylactic myeloid growth factor support per guidelines above.

Neutropenic Fever		
ANC ≤ 1000/mm^3, fever ≥ 38.5°C	Hold MLN0128 until ANC > 1000/mm^3 and fever < 38.5°C. Resume MLN0128 according to the number of episodes that are resolved to Grade ≤1 or baseline values within 2 weeks: • First episode: resume MLN0128 at same dose and schedule. • Second episode: resume MLN0128 at same dose and schedule. • Third episode: reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles. • Fourth episode: reduce MLN0128 dose to the next lower dose level from the reduced or an intermediate dose level for all subsequent cycles. • Fifth episode: stop MLN0128 and discontinue subject from study. Consider use of prophylactic myeloid growth factor support per guidelines above.	Hold paclitaxel until ANC > 1000/mm^3 and fever < 38.5°C. Resume paclitaxel according to the number of episodes that are resolved to Grade ≤1 or baseline values within 2 weeks: • First episode: resume paclitaxel at same dose and schedule. • Second episode: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • Third episode: reduce paclitaxel dose by 25% from starting dose (60mg/m^2) for all subsequent cycles. • Fourth episode: reduce paclitaxel dose by 50% from starting dose (40 mg/m^2) for all subsequent cycles. • Fifth episode: stop paclitaxel and discontinue subject from study. Consider use of prophylactic myeloid growth factor support per guidelines above.

Thrombocytopenia		
Grade 1 (≥ 75,000/mm^3)	No change. Continue MLN0128 at same dose and schedule.	No change. Continue paclitaxel at same dose and schedule.
Grade 2 (50-74,999/mm^3)	No change. Continue MLN0128 at same dose and schedule	Hold paclitaxel until platelets > 75,000/mm^3 Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • ≤ 1 week—no change to paclitaxel • > 1 but ≤ 2 weeks of interrupting • > 2 weeks of interrupting planned therapy—stop paclitaxel and discontinue subject from study
Grade 3 (25–44,999/mm^3)	Hold MLN0128 until platelets > 75,000/mm^3 Resume MLN0128 based on timing of recovery within 2 weeks: • ≤ 1 week—no change to MLN0128 dose • > 1 but ≤ 2 weeks—reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles • > 2 weeks—stop MLN0128 and discontinue subject from study Platelet transfusions in the absence of bleeding should not be administered.	Hold paclitaxel until platelets > 75,000/mm^3 Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • ≤ 1 week—no change to paclitaxel • > 1 but ≤ 2 weeks of interrupting planned therapy—reduce paclitaxel dose by 25% for all subsequent cycles • > 2 weeks of interrupting planned therapy—stop paclitaxel and discontinue subject from study Platelet transfusions in the absence of bleeding should not be administered.
Grade 4 (< 25,000/mm^3)	Hold MLN0128 until platelets ≥ 75,000/mm^3 Resume MLN0128 according to the number of episodes that are resolved to Grade ≤ 1 or baseline values within 2 weeks: • First episode: resume MLN0128 at same dose and schedule. • Second episode: reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles. • Third episode: reduce MLN0128 dose to the next lower dose level from the first reduced dose or an intermediate dose level for all subsequent cycles. • Fourth episode: stop MLN0128 and	Hold paclitaxel until platelets ≥ 75,000/mm^3 Resume paclitaxel according to the number of episodes that are resolved to Grade ≤ 1 or baseline values within 2 weeks: • First episode: reduce paclitaxel by 25% from starting dose (60mg/m^2) for all subsequent cycles. • Second episode: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • Third episode: reduce paclitaxel dose by 50% from starting dose (40 mg/m^2) for all subsequent cycles. • Fourth episode: stop paclitaxel and discontinue subject from study. Platelet transfusions should be

	discontinue subject from study. Platelet transfusions should be administered prophylactically if platelets ≤ 10,000/mm^3 or as clinically indicated if there is bleeding.	administered prophylactically if platelets ≤ 10,000/mm^3 or as clinically indicated if there is bleeding.
Anemia		
≥ 2 g/dL decrease in Hgb from baseline	No change. Continue MLN0128 at same dosing and schedule, support with RBC transfusions as clinically indicated, and rule out bleeding. Continue or reduce MLN0128 dose according to the number of episodes that are resolved to ≤ Grade 1 or baseline values within 2 weeks: • First and second episodes: continue MLN0128 at same dose and schedule. • Third episode: reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles. • Fourth episode: Continue MLN0128 dose. at the previously reduced dose while paclitaxel dose is reduced again • Fifth episode: stop MLN0128 and discontinue subject from study. Consider erythropoietin growth factor support.	Hold paclitaxel, support with RBC transfusions as clinically indicated, and rule out bleeding. Resume paclitaxel according to the number of episodes that are resolved to Grade ≤ 1 or baseline values within 2 weeks: • First episode: resume paclitaxel at same dose and schedule. • Second episode: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • Third episode: continue paclitaxel at 60 mg/m^2 for all subsequent cycles when MLN0128 dose is reduced • Fourth episode: reduce paclitaxel dose by 50% from starting dose (40 mg/m^2) for all subsequent cycles. • Fifth episode: stop paclitaxel and discontinue subject from study. Consider erythropoietin growth factor support.
Hepatic		
Grade 1	No change. Continue MLN0128 at the same dose and schedule.	No change. Continue paclitaxel at the same dose and schedule.

Grade 2	Hold MLN0128 until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks. Resume MLN0128 based on timing of recovery: • ≤ 1 week—no change to MLN0128 dose • > 1 but ≤ 2 weeks—reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles • > 2 weeks—stop MLN0128 and discontinue subject from study A rise in indirect bilirubin with a normal direct bilirubin believed to be attributable to Gilbert's disease does not require a change or hold in MLN0128 dosing. Gilbert's disease should be documented in the subject's medical history CRF page.	Hold paclitaxel until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks of interrupting planned therapy. Resume paclitaxel based on time of recovery: • ≤ 1 week—no change to paclitaxel dose • > 1 but ≤ 2 weeks of interrupting planned therapy—reduce paclitaxel dose by 25% for all subsequent cycles • > 2 weeks of interrupting planned therapy—stop paclitaxel and discontinue subject from study A rise in indirect bilirubin with a normal direct bilirubin believed to be attributable to Gilbert's disease does not require a change or hold in MLN0128 dosing. Gilbert's disease should be documented in the subject's medical history CRF page.
Grade ≥3	Hold MLN0128 until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks. Resume MLN0128 according to the number of episodes that are resolved to ≤ Grade 1 or baseline values: • First episode: resume MLN0128 at the same dose and schedule. • Second episode: reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles. • Third episode: reduce MLN0128 dose to the next lower dose level from the reduced dose or an intermediate dose level for all subsequent cycles. • Fourth episode: stop MLN0128 and discontinue subject from	Hold paclitaxel until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks of interrupting planned therapy. Resume paclitaxel according to the number of episodes that are resolved to ≤ Grade 1 or baseline: • First episode: reduce paclitaxel dose by 25% (60 mg/m^2) from starting dose for all subsequent cycles. • Second episode: reduce paclitaxel dose by 25% (60 mg/m^2) from starting dose for all subsequent cycles. • Third episode: reduce paclitaxel dose by 50% (45 mg/m^2) from starting dose for all subsequent cycles. • Fourth episode: stop paclitaxel and discontinue subject from study.

	study.	
Renal (Creatinine)		
Grade 1 (> ULN-1.5x ULN or > 1-1.5 x baseline)	No change. Continue MLN0128 at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, creatinine	No change. Continue paclitaxel at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, creatinine
Grade 2 (>1.5-3x ULN or >1.5-3.0 x baseline)	Hold MLN0128 until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, creatinine Consider IV hydration. Resume MLN0128 based on timing of recovery: • ≤ 1 week—no change to MLN0128 dose • > 1 but ≤ 2 weeks—reduce MLN0128 to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles • > 2 weeks—stop MLN0128 and discontinue subject from study	Hold paclitaxel until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks of interrupting planned therapy. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, creatinine Consider IV hydration. Resume paclitaxel at the same dose and schedule.
Grade ≥ 3 (>3-6x ULN/>3 baseline or >6 ULN)	Hold MLN0128 until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7	Hold paclitaxel until creatinine improves to ≤ Grade 1 or baseline values ≤ 2 weeks of interrupting planned therapy. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7

	• Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, creatinine Consider IV hydration. Resume MLN0128 based on timing of recovery: • ≤ 1 week—no change to MLN0128 dose • > 1 but ≤ 2 weeks—reduce MLN0128 to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles • > 2 weeks—stop MLN0128 and discontinue subject from study	• Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, creatinine Consider IV hydration. Resume paclitaxel based on timing of recovery: • ≤ 1 week—no change to paclitaxel dose • > 1 but ≤ 2 weeks of interrupting planned therapy—reduce paclitaxel dose by 25% for all subsequent cycles • > 2 weeks of interrupting planned therapy—stop paclitaxel and discontinue subject from study
Peripheral Neuropathy		
Grade ≤ 2	No change. Continue MLN0128 at same dose and schedule.	No change. Continue paclitaxel at same dose and schedule.

Grade ≥ 3	Continue MLN0128 during the first week when paclitaxel treatment is interrupted.
	
	• If peripheral neuropathy does not improve to Grade ≤ 2 after one week of paclitaxel treatment interruption, hold MLN0128 for one week
	  • Resume MLN0128 at the next lower dose level or an intermediate dose level that is between the current and next lower dose if the event recovers to Grade ≤ 2 after one week of MLN0128 interruption (two weeks of paclitaxel interruption)
	
	• Stop MLN0128 if the event does not recover to Grade ≤ 2 after one week of MLN0128
		Hold planned paclitaxel for one week to see if peripheral neuropathy improves to Grade ≤ 2.
		• Reduce paclitaxel dose by 25% for all subsequent cycles if peripheral neuropathy improves to Grade ≤ 2 after one week of paclitaxel planned treatment interruption
		
		• If peripheral neuropathy does not improve to Grade ≤ 2 after one week of planned paclitaxel treatment interruption, continue to hold paclitaxel treatment while MLN0128 treatment is held
		  ○ Resume paclitaxel by 25% dose reduction for all subsequent cycles if the event recovers to Grade ≤ 2 after two weeks of paclitaxel interruption (one week of MLN0128 interruption)
		
		• Stop paclitaxel if the event does not recover to Grade ≤ 2 after two weeks of planned paclitaxel treatment interruption (one week of MLN0128 interruption)

	interruption (two weeks of paclitaxel interruption)	
Hyperglycemia		
Grade ≤ 2 ULN – 250 mg/dL	Continue MLN0128 at same dose and schedule. Refer to Section 7.2.7 for guidelines on hyperglycemia management.	Continue paclitaxel at same dose and schedule. Refer to Section 7.2.7 for guidelines on hyperglycemia management.
Grade ≥ 3 >250 mg/dL	Hold MLN0128 until hyperglycemia improves to Grade ≤ 2. Refer to Section 7.2.7 for guidelines on hyperglycemia management. Optimize hyperglycemia therapy and resume MLN0128 based on timing of recovery: • ≤ 1 weeks – resume MLN0128 at same dose and schedule • > 1 but ≤ 2 weeks – reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles • > 2 weeks – stop MLN0128 and discontinue subject from study	Continue paclitaxel at same dose and schedule. Refer to Section 7.2.7 for guidelines on hyperglycemia management.
Rash		
Grade ≤ 2	Continue MLN0128 at same dose and schedule. Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	Continue paclitaxel at same dose and schedule. Consider treatment with topical steroid cream/ointment and/or oral antihistamines.
Grade ≥ 3	Hold MLN0128 until rash improves to Grade ≤ 2. Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or oral pulse steroids. Resume MLN0128 based on timing of recovery: • ≤ 2 weeks – reduce MLN0128 dose to the next lower dose level or an intermediate dose level that is between the current and next lower dose for all subsequent cycles • > 2 weeks – stop MLN0128	Continue paclitaxel at same dose and schedule. Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or oral pulse steroids.

	and paclitaxel and discontinue subject from study	

7.2.6.2 Dose Modification for Trastuzumab-Related Toxicities

During the expansion phase of the study, subjects in Arm B will receive trastuzumab in combination with MLN0128P at the $MTD^{MLN0128P}$. There is no dose reduction schedule for trastuzumab administration in this study. If an AE is assessed by the Investigator as mainly related to trastuzumab, such as congestive heart failure, trastuzumab administration should be held and appropriate measures taken per standard clinical practice and per the FDA label. If the subject's cardiac dysfunction does not recover back to baseline after 4 weeks of withholding trastuzumab and trastuzumab will be permanently discontinued, MLN0128 and paclitaxel should also be discontinued and the subject taken off the study. Table 7.4 below provides guidelines on the management of trastuzumab-related cardiotoxicity in subjects receiving MLN0128PH. If an adverse event may be related to the combination of MLN0128PH, the guidelines provided in Table 7.3 above may be followed for dose modification and/or delay of MLN0128 and/or paclitaxel.

Table 7.4 Guidelines for MLN0128, Paclitaxel, and Trastuzumab Dose Modification and Delay Due to Cardiotoxicity

Adverse Event	MLN0128	Paclitaxel	Trastuzumab
Asymptomatic decline in • LVEF > 15% from baseline values OR • LVEF 10-15% from baseline values and is below institution's LLN	No change. Continue MLN0128 at same dose and schedule.	No change. Continue paclitaxel at same dose and schedule.	Hold trastuzumab for 4 weeks. Reassess LVEF at 4 weeks: • If LVEF has recovered to baseline or absolute decline from baseline is < 15%, resume trastuzumab at same dose and schedule. • If LVEF has not recovered back to baseline or absolute decline from baseline is > 15%, stop trastuzumab, MLN0128, and paclitaxel and discontinue the subject from the study.
Symptomatic cardiac dysfunction/congestive heart failure	Stop MLN0128, paclitaxel, and trastuzumab and discontinue the subject from the study.		

7.2.7 Management of Hyperglycemia

In addition to obtaining fasting serum glucose (FSG) levels at the clinic visits as outlined in the Schedule of Events, all subjects will be given a glucometer to monitor their daily pre-dose fasting blood glucose (FBG) levels at home. Subjects will be instructed to notify the study staff immediately with any abnormal readings for further instructions on the management of their hyperglycemia.

In the event that any FSG reading performed at the site indicates hyperglycemia (> upper limit of normal [ULN]), the study staff should first ascertain that the subject was fasting at the time of the blood draw (ie, nothing by mouth for at least 8 hours prior to blood being obtained) and repeat the FSG as needed. If the repeat FSG continues to demonstrate hyperglycemia, Investigators should initiate steps to aggressively manage the hyperglycemia per standard clinical practice. The following guidelines are provided to aid the Investigator in initiating antiglycemic therapies.

All subjects developing hyperglycemia on the study should have their glucose closely monitored by study staff. The Investigator may choose to continue monitoring subjects with Grade 1 hyperglycemia (FSG > ULN ≤ 160 mg/dL) or consider initiating treatment with an oral hypoglycemic agent, such as metformin. All subjects with Grade ≥ 2 hyperglycemia (FSG > 160 mg/dL) should be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. The Investigator should consult an endocrinologist if needed to aid in optimizing the subject's hyperglycemia treatment plan. Refer to Table 7.3 above for guidelines on dose modification and/or delay of MLN0128 and paclitaxel.

It is recommended that subjects be initially treated with a fast acting, insulin sensitizer such as metformin at 500 mg orally (PO) QD and titrate up to a maximum of 1000 mg PO twice a day(BID) as needed. Concurrent addition to metformin of dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution due to the higher risk of inducing hypoglycemia in subjects. The dose of oral hypoglycemic agents should be adjusted in subjects with renal insufficiency.

In the ongoing phase 1 trial of MLN0128 as a single agent in subjects with advanced malignancies (Study INK128-001), most episodes of hyperglycemia observed have been Grades 1 and 2 that have responded quickly to oral metformin. Since instituting a standard regimen for the early treatment of hyperglycemia, no further episodes of Grade 3 hyperglycemia have been observed.

7.2.8 Subjects with Possible Cardiac Instability

For subjects showing signs of cardiac instability after MLN0128 dosing, additional monitoring on-site before clinic discharge should be considered.

7.3 Discussion of Study Design, Including Choice of Control Group

The proposed study design is standard for Phase I human oncology trials assessing safety and tolerability. Neither a placebo nor an active control will be included in this study.

7.4 Selection of Study Population

7.4.1 Inclusion Criteria

Individuals eligible to participate in either the dose escalation phase or the expansion phase of the study must meet all of the following inclusion criteria:

1 Age ≥ 18 years, including males and females;

2 Subjects must have locally advanced or metastatic solid tumors with the exception of primary brain tumor, and have failed or are not eligible for standard of care therapy. Subjects with a history of brain metastasis are eligible for the study as long as they meet all the following criteria: their brain metastases have been treated, they have no evidence of progression or hemorrhage after treatment, have been off dexamethasone for 4 weeks prior to first study drug administration, and have no ongoing requirement for dexamethasone or anti-epileptic drugs;

3 For Arm A of the expansion phase only, subjects with advanced bladder cancer or endometrial cancer will be enrolled and must have received at least 1, but no more than 2 prior lines of systemic therapy, including adjuvant or hormonal therapy;

4 For Arm B of the expansion phase only, HER2+ cancer is defined as a pathologic diagnosis of cancer which is 3+ by immunohistochemistry (IHC) for HER2 or positive for HER2 gene amplification by fluorescence in situ hybridization (FISH) and subjects must have received at least 1, but no more than 4 prior lines of systemic cytotoxic chemotherapy, excluding adjuvant, hormonal, or targeted therapy;

5 Subjects must have received no more than 4 prior lines of systemic cytotoxic chemotherapy for advanced or metastatic disease;

6 Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1;

7 Subjects must have adequate organ function, including the following:

   a. Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥ 1.5 x10^9/L; platelet count ≥ 100 x 10^9/L; hemoglobin ≥ 9 g/dL without transfusion in the last 2 weeks;

   b. Hepatic: total bilirubin ≤ 1.5 x upper ULN, transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) ≤ 2.5 x ULN (< 5 x ULN if liver metastases are present);

   c. Renal: normal serum creatinine or calculated creatinine clearance ≥ 60 mL/min (Cockroft - Gault formula);

   d. Metabolic: fasting serum glucose ≤ 130 mg/dL and fasting triglycerides ≤ 300 mg/dL;

8 Left ventricular ejection fraction (LVEF) ≥ 5 absolute percentage points below institutional standard of normal as measured by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) within 4 weeks prior to first study drug administration (ie, if the institutional normal is 50%, subject's LVEF may be as low as 45% to be eligible for the study);

9 For women of child-bearing potential, negative serum pregnancy test within 14 days

prior to the first study drug administration and use of physician-approved method of birth control from 30 days prior to the first study drug administration to 90 days following the last study drug administration;

10 Male subjects must be surgically sterile or must agree to use physician-approved contraception during the study and for 90 days following the last study drug administration;

11 Ability to swallow oral medications;

12 Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures;

7.4.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in either the dose escalation phase or the expansion phase of the study:

1 Diagnosis of primary brain tumor;

2 Have received prior cancer or other investigational therapy within 2 weeks prior to the first administration of study drug. For prior therapies with a half life longer than 3 days, the interval must be at least 28 days prior to the first administration of study drug and the subject must have documented disease progression. For prior trastuzumab therapy in subjects who enroll in Arm B of the expansion phase, the interval since the previous trastuzumab dose must be at least 7 days;

3 Have initiated hematopoietic growth factors within 1 week prior to the first administration of study drug; subjects already receiving hematopoietic growth factors on a chronic basis for ≥ 4 weeks are eligible;

4 Chronic systemic corticosteroid (except inhalers) use within 1 week prior to the first administration of study drug. Premedication with dexamethasone prior to paclitaxel administration in this study is allowed;

5 Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128;

6 Poorly controlled diabetes mellitus defined as HbA1c > 7%; subjects with transient glucose intolerance due to corticosteroid administration are allowed in this study if all other inclusion/exclusion criteria are met;

7 Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system (CNS) disease, active infection, or any other condition that could compromise the subject's participation in the study;

8 Known human immunodeficiency virus (HIV) infection;

9 Pregnancy (positive serum or urine pregnancy test) or breast feeding;

10 Any history of unstable angina, myocardial infarction, New York Heart Association (NYHA) Class III or IV heart failure (See Appendix C), and/or pulmonary hypertension;

11 Significant active cardiovascular disease including:

- Uncontrolled high blood pressure (ie, systolic blood pressure >180 mm Hg, diastolic blood pressure > 95 mm Hg)

- Grade 3 or higher valvular disease
- Grade 3 or higher atrial fibrillation
- Grade 3 or higher bradycardia
- Endocarditis
- Pulmonary embolism
- Recent cerebrovascular accident within 6 months prior to enrollment

12 A requirement for inotropic support or serious uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation) within 1 year prior to screening

13 A pacemaker or implantable cardiac defibrillator;

14 Baseline prolongation of the rate-corrected QT interval (QTc) (eg, repeated demonstration of QTc interval > 480 milliseconds) (See Section 7.8.2.2);

15 History of congenital long QT syndrome, ventricular fibrillation, ventricular tachycardia or torsades de pointes.

Other Considerations for Exclusion

Patients taking strong CYP3A4, and CYP2C19 inhibitors and/or inducers should be considered with caution. Alternative treatments that are less likely to affect MLN0128 metabolism, if available, should be considered. If a patient requires treatment with one or more of the strong CYP3A4, and CYP2C19 inhibitors and/or inducers, the medical monitor should be consulted. Examples of the strong CYP3A4 and CYP2C19 inhibitors and inducers include (see Appendix B):

Strong inhibitors:

CYP3A4: Ketoconazole, itraconozole, ritonavir, mibefradil indinavir, clarithromycin

CYP2C19: Fluconazole, fluvoxamine, omeprazole, ticlopidine

Strong inducers:

CYP3A4: Rifampin (also a moderate CYP2C19 inducer), phenytoin, carbamazepine, St. John's wort

Patients should not consume food or beverages containing the fruit or juice from grapefruits, pomegranates, star fruit, papayas, or Seville oranges within 7 days before first dose of study drug.

7.4.3 Removal of Subjects from Treatment or Assessment

Subjects may withdraw their consent to participate in this study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the Termination visit should be carried out.

Millennium must be notified of all subject withdrawals as soon as possible. Millennium also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

Reasons for which the Investigator or Millennium may withdraw a subject from the study include, but are not limited to, the following:

- Subject experiences disease progression
- Subject experiences unacceptable toxicity, ie
  - Subject develops an AE which meets the DLT definition but the AE does not resolve to Grade ≤ 1 within 28 days despite optimal treatment per standard clinical practice
  - Subject requires more than 2 dose reductions
- Subject experiences toxicity that is determined by the Investigator to be no longer safe for the subject to continue therapy
- Subject requests to withdraw from the study treatment
- Subject requires or has taken medication prohibited by the protocol
- Subject is unwilling or unable to comply with the study requirements
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up
- Subject becomes pregnant

Subjects will return for a Termination visit within 30 days after the last administration of MLN0128 or paclitaxel or trastuzumab, whichever is discontinued last. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after 2 attempts, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information should be recorded in the study records.

Prior to enrollment into the study, the Investigator or designee must explain to each subject that the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB in order to analyze and evaluate study results. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as HIPAA in the US, from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

7.4.4 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier by the Sponsor or designee. This unique identifier will be on all CRF pages. During dose escalation, subjects who discontinue treatment before completing ≥ 75% of planned MLN0128 doses in Cycle 1 for reasons other than study drug-related toxicity will be replaced.

7.5 Treatments

7.5.1 Treatments Administered

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

In the absence of unacceptable MLN0128P or MLN0128PH treatment-related toxicity or disease progression, subjects may receive MLN0128P or MLN0128PH treatment for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor. Subjects will remain on study as long as they continue to receive MLN0128, paclitaxel, or trastuzumab without additional anticancer therapies. Millennium and its designee will provide the study site with a supply of MLN0128 sufficient for the completion of the study.

7.5.2 Identity of Investigational Product (IP) MLN0128

MLN0128 is a small molecule being developed as a potent, selective inhibitor of mTORC1/2 for the treatment of subjects with advanced solid tumors and hematologic malignancies.

7.5.2.1 MLN0128 Product Characteristics

MLN0128 may be supplied in tamper-resistant bottles as capsules containing 1 of 4 dose strengths.

- MLN0128 capsules, 1 mg
- MLN0128 capsules, 3 mg
- MLN0128 capsules, 5 mg

Each 1 mg, 3 mg, and 5 mg capsule for oral administration contains 1 mg, 3 mg, and 5 mg MLN0128 respectively and the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant), and hard gelatin capsule.

7.5.3 Storage and Labeling of MLN0128

At a minimum, each bottle label shipped to the sites will provide the following information: batch number/lot number, study identification, required storage conditions, directions for use, and region specific caution statements (including “New Drug – Limited by United States federal law to investigational use” language).

MLN0128 accountability records will be maintained by the pharmacy or designated drug preparation area at the study site. Upon receipt of MLN0128 supplies, the pharmacist or a designated study staff will inventory the MLN0128 supplies and complete the designated section of the shipping form. The shipping/inventory form must be sent to Millennium or its designee, as instructed.

MLN0128 should be stored at controlled room temperature 15 to 30 °C (59 to 86 °F). All study supplies must be kept in a restricted access area.

A complete dispensing log must be maintained for all MLN0128 dispensed and all capsules of MLN0128 must be accounted for.

7.5.4 Directions for Administration of Study Medications

7.5.4.1 MLN0128

Prior to Amendment 1, MLN0128 was to be initially administered orally on a QDx3d QW schedule. On days when weekly paclitaxel was administered (Days 1, 8 [±1 day], and 15 [±1 day] of every 28-day cycle), MLN0128 was to be administered in the clinic within 30 minutes of the completion of paclitaxel infusion. With implementation of Amendment 1, alternate dosing schedules (such as QDx5d QW) of MLN0128 administration in combination with paclitaxel may be evaluated to optimize tolerability and exposure of the combination. For the intermittent dosing schedules (such as QDx3d QW or QDx5d QW), in subsequent dose escalation cohorts, MLN0128 will be administered at approximately 24 hours following completion of paclitaxel infusion. For example, on the QDx3d QW dose schedule, paclitaxel will be administered on Days 1, 8 (±1 day), and 15 (±1 day) and MLN0128 will be administered on Days 2-4, 9-11, 16-18, and 22-24 of every 4-week cycle. Likewise, on the QDx5d QW dose schedule, paclitaxel will be administered on Days 1, 8 (±1 day), and 15 (±1 day) and MLN0128 will be administered on Days 2-6, 9-13, 16-20, and 22-26 of every 4-week cycle.

If paclitaxel administration is altered by ±1 day, MLN0128 administration should also be altered accordingly.

On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 will be administered alone for subjects receiving MLN0128P and within 30 minutes of the completion of trastuzumab for subjects receiving MLN0128PH. Cycles are repeated every 28 days.

On each clinic day, the site will administer MLN0128 to the subject (the subject should be counseled not to take their MLN0128 dose at home on the day of the clinic visit). Subjects will take their prescribed dose orally once in the morning with a meal at approximately the same time of day except on Cycle 1 Day 1 (prior to Amendment 1) or Cycle 1, Day 2 (upon implementation of Amendment 1), which requires a fasting glucose level post-MLN0128 dose. At this visit, subjects should be dosed with MLN0128, have the fasting glucose drawn, and then be allowed to eat a meal. In cases where a subject misses dosing at his/her dosing time, the subject may still take the dose within 12 hours of the regular dosing time with a meal (subjects should not take 2 consecutive daily doses within 12 hours of each other). Subjects who vomit shortly after receiving MLN0128 will not receive a replacement dose. If confirmed that the study drug has been vomited, the dose should be noted as having been missed.

MLN0128 capsules should not be opened or crushed. Direct contact with the powder in MLN0128 capsules with skin or mucous membranes should be avoided. If such contact occurs, the subject should wash thoroughly with water.

MLN0128 capsules should be swallowed with water without chewing or sucking the capsule. If the subject chews or sucks the capsules by error, the subject should drink a large glass of water (~8 oz).

Prophylactic use of anti-emetic, anti-nausea, and anti-diarrheal medications is encouraged and may be used prior to each MLN0128 dosing as needed throughout the study. Additional details will be provided in the Pharmacy Manual.

7.5.4.2 Paclitaxel Administration

Paclitaxel will be administered weekly according to institutional standard of care.

Paclitaxel will be administered on Days 1, 8 (±1 day), and 15 (±1 day) of each cycle at a dose of 80 mg/m^2 as a 1-hour infusion or according to the institutional standard of care for weekly paclitaxel administration. If a subject's body weight increases or decreases by ≥ 10% from baseline during the course of the study, the body surface area and drug dose should be recalculated.

All subjects should be premedicated before treatment with paclitaxel according to institutional standards (eg, dexamethasone 20 mg orally, administered approximately 12 and 6 hours before beginning the paclitaxel infusion or dexamethasone 20 mg IV 30 minutes before the beginning the paclitaxel infusion; diphenhydramine 12.5 mg- 50 mg IV 30 to 60 minutes before the infusion; and cimetidine 300 mg IV/PO or ranitidine 50 mg IV or 150 mg PO, or famotidine 20mg IV/PO 30 to 60 minutes before the infusion). If dexamethasone is used, subjects should be closely monitored for hyperglycemia and treated as needed per standard clinical practice and according to the guidelines in Section 7.2.7. On days of paclitaxel infusion, MLN0128 will be given orally in the clinic within 30 minutes (prior to Amendment 1) of the completion of paclitaxel infusion. Upon implementation of Amendment 1, MLN0128 will be given orally in the clinic or at home approximately 24 hours following paclitaxel infusion. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 will be administered alone for subjects receiving MLN0128P and within 30 minutes of the completion of trastuzumab for subjects receiving MLN0128PH.

7.5.4.3 Trastuzumab Administration

Trastuzumab will be administered weekly to subjects with Her2+ cancer enrolled in the expansion Arm B.

A loading dose of trastuzumab 4 mg/kg will be given IV over 90 minutes on C1D1, followed by 2 mg/kg IV over 30 minutes weekly thereafter. For subjects entering expansion Arm B who are already receiving trastuzumab, the Cycle 1, Day 1 dose will be 2 mg/kg IV if the previous trastuzumab dose had been administered within the last 28 days. If the last trastuzumab dose was administered more than 28 days before Cycle 1, Day 1, then the 4-mg/kg loading dose will be administered. Trastuzumab will be administered intravenously on Days 1, 8 (±1 day), 15 (±1 day) and 22 (±1 day) of every 28-day cycle prior to paclitaxel administration according to FDA approved label and institution's standard clinical practice. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 will be administered within 30 minutes of the completion of

trastuzumab for subjects receiving MLN0128PH. All treatment doses should be based on actual body weight and not ideal body weight. If a subject's body weight increases or decreases by ≥ 10% from C1D1 during the course of the treatment phase, the drug dose should be recalculated.

7.5.5 MLN0128-related Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Millennium or designee and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Sponsor's Quality representative.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and submitted as described in Section 8.2.

7.5.6 Method of Assigning Subjects to Treatment Groups

The enrollment and treatment assignment will be centrally managed by Millennium and its designee. When a treatment cohort is open for enrollment, sites will fax in a Subject Registration Form along with subject eligibility supporting documents for each potential subject to Millennium and its designee. Millennium and its designee will assign a subject number and treatment cohort for each subject that is accepted into the study. Sites cannot enroll or start dosing the subject without receiving the assigned subject number and treatment cohort from Millennium or its designee. In the event that more than 1 dosing arm is open for enrollment during the dose escalation phase, then a randomization schema provided by the biostatistician will be used to assign subjects to a dosing schedule. Subjects may not participate in more than 1 dosing arm.

7.5.7 Selection of MLN0128 Doses Used in the Study

The starting dose of MLN0128 for this study is 6 mg daily for the first three days of each week. If a DLT is observed in 2 or more subjects in a cohort of 3 to 6 subjects treated with the starting dose of 6 mg, a new cohort of 3to 6 subjects will be enrolled at either 4 mg or an intermediate dose level between 4 mg and 6 mg.

Dose escalation will be according to a modified Fibonacci schema. For example, a starting dose of 6 mg may be escalated in successive cohorts to 8 mg, 10 mg, etc. or an intermediate dose between 2 planned doses may be evaluated. The level of dose escalation or a decision to go to an intermediate dose or a lower dose will be determined after discussion between the participating Investigators and Millennium's Medical Monitor prior to dose escalation, but will not exceed the planned next escalated dose according to the modified Fibonacci schema.

7.5.8 Selection of Timing of Dose of MLN0128 for Each Subject

The 2 ongoing phase 1 single agent MLN0128 studies in solid tumors and multiple myeloma are evaluating the safety, pharmacokinetics, and preliminary efficacy of daily dosing of MLN0128. Based on the limited clinical data available, dosing of MLN0128 QDx3d QW should provide similar PK parameters, with perhaps a better tolerability profile. The dosing schedules herein are based on an understanding of the proposed mechanism of action of MLN0128 as an mTORC1/mTORC2 inhibitor and a desire to avoid interference with paclitaxel. MLN0128 has been shown to induce G1 cell cycle arrest. Paclitaxel is known to block the progression of cells through G2 into mitosis and this G2-M arrest has been proposed to be a prerequisite step for apoptosis induced by paclitaxel (Shu et al, 1997). Pretreatment of mTOR inhibitors will arrest cells in G1 phase and antagonize the toxic effect of paclitaxel (Mondesire et al, 2004). Therefore, MLN0128 should be given after paclitaxel administration in order not to interfere with the mechanism of paclitaxel. Amendment 1 will evaluate additional dosing schedules for MLN0128 administration in combination with paclitaxel (such as QDx5d QW dosing) to maximize tolerability and exposure of the doublet combination. Recent preclinical in vivo xenograft data also suggest that administration of MLN0128 approximately 24 hours, instead of within 30 minutes, following paclitaxel infusion may provide more synergy in tumor cell kill; therefore, for subsequent cohorts opened following Amendment 1, MLN0128 will be administered approximately 24 hours following paclitaxel administration. Once Amendment 1 is implemented at a given site, all active patients at that site will convert to this new timing at the start of the next cycle.

7.5.9 Blinding

This is an open label study with no placebo or comparators.

7.5.10 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a subject within 30 days before the first study drug administration will be recorded on the designated CRF.

The following medications/therapies are prohibited during the study:

- Other investigational agents or mTOR inhibitors
- Other anticancer therapies including radiation or surgery (palliative radiation for pain control of pre-existing lesions is allowed with Sponsor approval)
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers or premedication with dexamethasone prior to paclitaxel administration) during the dose escalation phase of the study, unless necessary for treatment of MLN0128-related AE, ie, rash
- Anti-epileptic drugs for subjects with treated brain metastasis
- Strong CYP3A4 /CYP2C19 inducers/inhibitors (see Appendix B)

If a patient requires treatment with one or more of the strong CYP3A4, and CYP2C19 inhibitors and/or inducers, the medical monitor should be consulted. Examples of the strong CYP3A4 and CYP2C19 inhibitors and inducers can be found in Appendix B.

There are no known strong specific CYP2C9 inhibitors or inducers. Examples of moderate inhibitors of CYP2C9 are fluconazole and miconazole; and moderate inducers of CYP2C9 are carbamazepine and rifampin (Appendix B). These agents show some degree of overlap with their modulation of CYP3A4 and CYP2C19 activity and should hence be considered with similar caution.

Patients should not consume food or beverages containing the fruit or juice from grapefruits pomegranates, star fruit, papayas, or Seville oranges within 7 days before first dose of study drug or at anytime while on study.

Prophylactic use of anti-emetic, anti-nausea, and anti-diarrheal medications is encouraged and may be used prior to first dose of study drug (paclitaxel and MLN0128), and as needed throughout the study prior to each dosing and as clinically indicated per standard practice. If dexamethasone is used, subjects need to be closely monitored for hyperglycemia and treated as needed per standard clinical practice and according to the guidelines in Section 7.2.7.

Myeloid growth factors, transfusions of blood and other blood products should not be used prophylactically prior to dosing of the study medications during Cycle 1 except as clinically indicated, but may be administered per standard clinical practice during the course of the study as needed.

Concurrent bisphosphonate use is allowed if bisphosphonate was initiated prior to the first administration of MLN0128. Bisphosphonates should be given after Cycle 1 to minimize confounding factors which may contribute to potential drug-related toxicities. Renal function should be monitored closely in subjects receiving bisphosphonate therapy. Subjects will be discontinued from the study if a new bisphosphonate needs to be started while on study for new metastatic bone lesions.

Other medications considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator. Any concomitant medications added or discontinued during the study should be recorded on the CRF.

7.5.11 Treatment Compliance

The importance of treatment compliance should be emphasized to the subject. Subjects will be given enough MLN0128 to dose between visits as well as detailed instructions on how to take medications at home. Subjects will be instructed to return all used and unused study drug containers at each study visit. Subject compliance with the dosing regimen will be assessed by reconciliation of the used and unused study drug at each clinic visit. The quantity dispensed, returned, used, lost, etc. will be documented by site personnel on the appropriate form. The site personnel will clarify any discrepancies in drug accountability with the subject and treatment compliance should be verified before dispensing new study medication to the subject.

7.6 Investigational Product Accountability

The Principal Investigator (PI) or designee is responsible for maintaining accurate drug accountability records (including dates and quantities) of MLN0128 received, subjects to whom

IP is dispensed (subject-by-subject dose specific accounting), and IP lost or accidentally or deliberately destroyed. The PI or designee must retain all unused or expired study supplies until the Millennium-designated CRA has confirmed the accountability data.

7.6.1 Return and Disposition of Clinical Supplies

Unused MLN0128 must be kept in a secure location until it can be reconciled by the Millennium-designated CRA. The Millennium-designated CRA must account for all study drug in a formal reconciliation process prior to study drug destruction. Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after Millennium or its designee has granted approval for drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to Millennium or its designee and retained in the PI's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to Millennium's designee upon request. The return of study drug or study drug materials must be documented according to instructions provided by Millennium's designee.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

7.7 Dietary or Other Protocol Restrictions

No dietary restrictions will be imposed on study subjects other than avoiding the fruit and fruit juices outlined in Appendix B.

7.8 Efficacy and Safety Variables

7.8.1 Efficacy and Safety Measurements Assessed

The Schedule of Events in the Synopsis (Section 2.1) describes the timing of required evaluations.

7.8.2 Safety Variables

Safety will be assessed by periodic physical examinations, 12-lead ECGs (see Section 7.8.2.1, clinical laboratory assessments, in-home monitoring of glucose levels via a glucometer and monitoring of AEs.

Any abnormal clinical laboratory test results determined to be clinically significant by the Investigator should be repeated (at the Investigator's discretion) until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

All clinical laboratory result pages should be initialed and dated by an Investigator, along with a comment regarding whether or not the result is clinically significant.

The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the AE CRF.

Adverse events will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

7.8.2.1 Acquisition of 12-Lead Electrocardiograms

All scheduled ECGs should be performed after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of ECG assessments coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.

7.8.2.2 Review of 12-Lead Electrocardiograms

To ensure safety, a qualified individual at the site will review any clinically significant ECG abnormalities, including confirmation that the machine-estimates of the QTc are accurate using the appropriate QT correction formula. In the event that a QTc value confirmed by the qualified reader is > 480 msec, an evaluation should be conducted to correct other possible causes (eg, electrolyte disturbance, concomitant medication, etc.). A list of medications known to prolong QTc can be found at www.torsades.org and www.QTdrugs.org. If done prior to protocol enrollment and if a repeat ECG meets eligibility requirements, the patient may enroll to the study upon review and agreement by the medical monitor.

7.8.2.3 Review of Clinically Significant Electrocardiographic Abnormalities

In the event that a QTc value confirmed by the qualified reader is > 500 msec for any ECG, the following will occur:

- The sponsor's medical monitor will be promptly notified.
- MLN0128 should be interrupted and an evaluation should be conducted to correct other possible causes (eg, electrolyte disturbance, concomitant medication).
- A formal consult by a cardiologist should be considered. Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall are below the threshold interval that triggered the repeat measurement.

The decision on whether to reinitiate MLN0128 treatment with or without dose reduction and additional monitoring in those patients who had asymptomatic prolonged QTc > 500 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated MLN0128, and appear to have benefitted from MLN0128 treatment with either disease control or response, will be agreed to by the investigator and the medical monitor on a case-by-case basis.

7.8.3 Efficacy Variables

Radiographic and/or physical assessments of the malignancies will be made at Screening/Baseline (within 28 days before the first study drug administration) and every 3 cycles (±7 days) thereafter. Objective response (complete response [CR] and partial response [PR]) as determined by the subject's best tumor response, duration of response, and time to progression will be assessed for all subjects using RECIST criteria version 1.1. A confirmatory CT/MRI scan should be performed at approximately 4 weeks from the previous scan for all patients with an objective response of ≥ PR.

7.8.4 Additional Variables

7.8.4.1 Pharmacokinetics

Additional variables to be examined as a part of this study include PK parameters such as C_{max}, C_{min}, T_{max}, AUC, and half-life of MLN0128 and paclitaxel in plasma. The additional intravenous PK parameters, clearance (CL) and volume of distribution (V_{ss}) will be estimated for paclitaxel. Comparisons across dose levels will be made to assess proportionality. In addition, comparison between single dose and multi-dose PK parameters will be made for assessment of steady-state drug accumulation.

7.8.4.2 Pharmacodynamics

7.8.4.2.1 Biomarkers of TORC1/2 Target Inhibition

CCI

[redacted]

7.8.4.2.2 Exploratory Apoptotic Biomarkers

CCI

[redacted]

CCI

[redacted]

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

8.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

8.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient or subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious

when, based on appropriate medical judgment, may jeopardize the patient or subject, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[12] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient or subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 8.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 8.1) must be reported (see Section 8.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE

or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information
Cognizant
United States and Canada
Toll-Free Fax #: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com
All Other Countries (Rest of World)
Fax #: 1-202-315-3560
Email: TakedaOncoCases@cognizant.com

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned). For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.0. The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding related or not related to this question: Is there a reasonable possibility that the AE is associated with the study drug?

8.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from administration of the first dose of study drug through 30 days after the administration of the last dose of study drug and recorded in the CRFs.

Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the CRF.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after the

administration of the last dose of study drug and recorded in the CRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

8.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male subject becomes pregnant during the male subject's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

9 APPROPRIATENESS OF MEASUREMENTS

9.1 Pharmacokinetics

The plasma concentrations for MLN0128 and paclitaxel will be determined using a liquid chromatography tandem mass spectrometry method. The measured MLN0128 and paclitaxel plasma concentrations will be used to determine the pharmacokinetic parameters of MLN0128 and paclitaxel, including AUC, C_{max}, C_{min}, T_{max}, and $t_{1/2}$. The additional intravenous PK parameters, CL and V_{ss} will be estimated for paclitaxel. Comparisons across dose levels will be made to assess proportionality. In addition, comparison between single dose and multi-dose PK parameters will be made for assessment of steady-state drug accumulation.

9.2 Biomarker Assessments

9.2.1 Pharmacodynamic Assessments

CCI

[redacted]

9.2.2 Assessments of Predictive Biomarkers of Activity

CCI

[redacted]

10 STUDY PROCEDURES

10.1 Screening and Baseline Assessments

An ICF must be obtained before any study-specific screening evaluations are performed and should be documented in the subject's medical chart.

The following evaluations and procedures will be performed within 28 days prior to the first study drug administration (Cycle 1 Day 1):

- Signed informed consent form for the Health Insurance of Portability and Accountability Act (HIPAA)
- Medical history (including demographics and prior cancer therapy)
- Concomitant medications
- Radiological assessments: CT (with contrast) or MRI scans of chest, abdomen and/or pelvis (the method used for a subject [CT or MRI] must be the same throughout the study)
- Tumor markers (eg, cancer antigen [CA]125, prostate-specific antigen [PSA], CA19-9, CA27.29, CA15.3 and carcinoembryonic antigen [CEA]) should be obtained within 4 weeks prior to first dose
- ECHO or MUGA

The subject must have discontinued all prior therapies according to the exclusion criteria and will have the following evaluations and procedures performed within 14 days prior to the first administration of study drug (Cycle 1 Day 1):

- Complete physical examination including height, weight, vital signs and ECOG performance status (see Appendix A)
- Concomitant medications
- Laboratory assessments
    - Hematology: complete blood count (CBC) with differential, hemoglobin, hematocrit, and platelet count
    - HbA1c
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, and fasting serum glucose.
    - Coagulation: PT/INR, PTT
    - Fasting serum lipid profile: total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted

  - Serum pregnancy for females of child-bearing potential only
- 12 -lead ECG (see Section 7.8.2.1)
- Archival tumor tissue (either paraffin blocks or a minimum of 10 unstained slides of archival tumor tissue for assessment of predictive/prognostic markers. Archival tumor tissues can be collected after the subject begins study drug treatment, if extra time is needed to locate the specimens).
- Tumor tissue biopsy only on subjects who have tumor tissue that is accessible for biopsy per the Investigator and who have signed the consent for tumor biopsy (see Tumor Biopsy Laboratory manual). This procedure can be done pre-dose on Cycle 1 Day 1, if it is not done during screening.

10.2 Treatment Visit(s)

If the subject meets all inclusion/exclusion criteria after the screening visit(s), the site will fax in the Subject Registration Form along with subject eligibility supporting documents to obtain a subject number and treatment cohort. Once the site receives the assigned subject number and treatment cohort, the subject will start paclitaxel 80 mg/m^2 intravenously (IV) weekly on Days 1, 8 (±1 day), and 15 (±1 day) of every 28-day cycle in combination with MLN0128 administered QDx3d QW or via alternate dosing schedules (such as QDx5d QW) of a the 4- week cycle. Prior to Amendment 1, on days when weekly paclitaxel is administered (Days 1, 8 [±1 day], and 15 [±1 day] of every 28-day cycle), MLN0128 was to be administered in the clinic within 30 minutes of the completion of paclitaxel infusion. Upon implementation of Amendment 1, MLN0128 will be administered approximately 24 hours following paclitaxel infusion. If paclitaxel dosing is altered ±1 day, MLN0128 administration should also be altered accordingly. The subject should not take MLN0128 at home on the days of the clinic visits. Subjects with HER2+ cancers in Arm B of the expansion phase will start trastuzumab weekly prior to the administration of paclitaxel on the days when weekly paclitaxel is administered. On Day 22 (±1 day) when paclitaxel is not administered, MLN0128 will be administered alone for subjects receiving MLN0128P and within 30 minutes of the completion of trastuzumab for subjects receiving MLN0128PH. The subject should not have anything by mouth (eat or drink except water) after midnight prior to the clinic visits when blood draws for fasting glucose or fasting lipid profile will be required. The subject will be given a glucometer to monitor daily pre-dose fasting glucose levels at home throughout the study. Subjects will be instructed to notify the study staff immediately with any abnormal readings (ie, fasting blood glucose ≥ 140 mg/dL).

10.2.1 Cycle 1

10.2.1.1 Cycle 1 Week 1

10.2.1.1.1 Cycle 1 Day1

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

The following assessments will be repeated if they were done more than 3 days prior to Cycle 1 Day 1:

- Complete physical examination including weight, vital signs and ECOG performance status (see Appendix A)
- 12 -lead ECG (see Section 7.8.2.1)
- Laboratory assessments
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted
    - Serum or urine pregnancy for females of child-bearing potential only
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting serum glucose (Electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing.)
- Concomitant medications
- Assessments of AEs

Paclitaxel and Trastuzumab Administration

Prior to Amendment 1 MLN0128 was to be administered within 30 minutes of completion of paclitaxel infusion. Upon implementation of Amendment 1, MLN0128 will be administered approximately 24 hours following paclitaxel infusion. Once Amendment 1 was implemented at a given site, all active patients at that site converted to this new timing at the start of the next cycle.

- Administration of paclitaxel for subjects receiving MLN0128P if results of hematology, CHEM-7 (BUN, creatinine, sodium, potassium, chloride, bicarbonate, and fasting serum glucose) and liver function tests (LFTs: ALT, AST, alkaline phosphatase, total bilirubin, and direct bilirubin) are acceptable
- Administration of trastuzumab and paclitaxel, respectively, for subjects receiving MLN0128PH if results of CBC, CHEM-7, and LFTs are acceptable

Procedures after Paclitaxel Administration:

- Plasma PK samples will be obtained for subjects in the dose escalation phase prior to determination of the $MTD^{MLN0128P}$: immediately at end of paclitaxel infusion (EOPI and pre-MLN0128 dose) and at 0.5 (±15 min) hour, 1 hour (±15 min), 2 hours (±30 min), 4 hours (±30 min), and 6 hours (±30 min) (see Pharmacokinetic Laboratory Manual).
- Assessments of AEs
- Concomitant medications

- Tumor biopsy for PD evaluation, if not done within 2 weeks prior to first dose

10.2.1.1.2 Cycle 1 Day 2

Subjects in the expansion phase are not required to return to clinic on this day. Subjects will take study medication at home per instructions.

The following assessments/procedures will be performed for subjects in the dose escalation phase.

Assessments prior to MLN0128 dosing:

- PK sample for 24 hours (±2 hours) after Cycle 1 Day 1 dosing only for subjects participating in the dose escalation phase of the study (see Pharmacokinetic Laboratory Manual)
- Fasting serum blood glucose
- Assessments of AEs
- Concomitant medications

MLN0128 Administration:

- Administer MLN0128 orally in clinic 24 hours after paclitaxel administration (subjects in the expansion phase will take MLN0128 at home per instructions).

Procedure(s) after MLN0128 dosing:

- Blood sampling for PK assessments only for subjects participating in the dose escalation phase prior to determination of the $MTD^{MLN0128P}$: at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (±30 min), 4 hours (±30 min), and 6 hours (±30 min) post-MLN0128 dose
- Fasting blood glucose at 1 (±15 min) hour post-MLN0128 dose
- ECG at 4 (±15 min) hours post-MLN0128 dose (see Section 7.8.2.1)
- Dispense MLN0128 and provide dosing instructions to the subject. Provide the subject with an in-home glucometer; train the subject on how to use the glucometer and instruct them to collect a daily pre-dose fasting glucose level every morning and to contact the site if a value is abnormal. The early detection and treatment of hyperglycemia has been key in managing this drug-related AE effectively in previous human studies with MLN0128. Each institution should decide an abnormal fasting glucose level (ie, ≥ 140 mg/dL) where treatment and close monitoring of hyperglycemia might be required.

10.2.1.2 Cycle 1 Week 2 (Cycle 1 Day 8±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Symptom-directed physical examination including weight, vital signs, and ECOG performance status (see Appendix A)

- 12 -lead ECG (see Section 7.8.2.1)
- Laboratory assessments
  - Hematology: CBC with differential, hematocrit, platelet count, and hemoglobin
  - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, and fasting serum glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
  - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycle 1 Day 8±1)

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7, and LFTs are acceptable
- Administration of trastuzumab and paclitaxel respectively for subjects receiving MLN0128PH if results of CBC, CHEM-7, and LFTs are acceptable

MLN0128 Administration (Cycle 1 Day 9±1):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion.

Procedure(s) after MLN0128 dosing:

- Tumor biopsy for PD evaluation 3 hr ±1 hr post-MLN0128 dose (any day between Days 9-16)
- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.1.3 Cycle 1 Week 3 (Cycle 1 Day 15±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Symptom directed physical examination including weight, vital signs and ECOG performance status (see Appendix A)
- 12 -lead ECG (see Section 7.8.2.1)

- Laboratory assessments
  - Hematology: CBC with differential, hematocrit, platelet count, and hemoglobin
  - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
  - Coagulation: PT/INR, PTT
  - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycle 1 Day 15±1)

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7, and LFTs are acceptable
- Administration of trastuzumab and paclitaxel respectively for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Cycle 1 Day 16±1):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion.

Procedure(s) after MLN0128 dosing:

- Tumor biopsy for PD evaluation 3 hr ±1 hr post-MLN0128 dose (any day between Days-9-16)
- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.1.4 Cycle 1 Week 4 (Cycle 1 Day 22±1)

Assessments prior to MLN0128 dosing for subjects receiving MLN0128P or prior to trastuzumab dosing for subjects receiving MLN0128PH (note, subjects will not receive paclitaxel at this visit):

- Symptom directed physical examination including weight, vital signs, and ECOG performance status (see Appendix A)
- 12 -lead ECG (see Section 7.8.2.1)

- Laboratory assessments
  - Hematology: CBC with differential, hematocrit, platelet count, and hemoglobin
  - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting glucose (electrolyte levels should be corrected as needed prior to MLN0128 or trastuzumab dosing)
  - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)
- Administration of trastuzumab for subjects receiving MLN0128PH

MLN0128 Administration

- Administer MLN0128 (after completion of trastuzumab infusion for subjects receiving MLN0128PH)

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.2 Cycle 2

10.2.2.1 Cycle 2 Week 1 (Cycle 2 Day 1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Complete physical examination including weight, vital signs and ECOG performance status (see Appendix A)
- 12 -lead ECG (see Section 7.8.2.1)
- Laboratory assessments
  - Hematology: CBC with differential, hematocrit, platelet count, and hemoglobin
  - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)

  - Coagulation: PT/INR, PTT
  - Fasting serum lipid profile: total cholesterol, HDL-C, LDL-C, triglycerides
  - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycle 2 Day 1±1)

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7 and LFTs are acceptable
- Administration of trastuzumab and paclitaxel respectively for subjects receiving MLN0128PH if results of CBC, CHEM-7, LFTs, and coagulation (PT/INR and PTT) are acceptable
- Plasma PK samples will be obtained for subjects in the dose escalation phase prior to determination of the $MTD^{MLN0128P}$: immediately at EOPI and pre-MLN0128 dose (see PK Laboratory Manual)

Procedure(s) after Paclitaxel Administration:

- Blood sampling for PK assessments only for subjects participating in the dose escalation phase of the study at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (±30 min), 4 hours (±30 min) and 6 hours (±30 min) after the dosing (see PK Laboratory Manual)
- Assessments of AEs
- Concomitant medications
- Return the glucometer to the subject for continued daily fasting glucose monitoring

10.2.2.2 Cycle 2 Week 1 (Cycle 2 Day 2)

Subjects in the expansion phase are not required to return to clinic on this day. Subjects will take study medication at home per instructions.

The following assessments/procedures will be performed for subjects in the dose escalation phase:

Assessments prior to MLN0128 dosing:

- PK sample at pre-dose

- Fasting blood glucose
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications

Administer MLN0128 orally in clinic.

Procedure(s) after MLN0128 dosing:

- Blood sampling for PK assessments only for subjects participating in the dose escalation phase prior to determination of the $MTD^{MLN0128P}$: at 0.5 hour (±15 min), 1 hour (±15 min), 2 hours (±30 min), 4 hours (±30 min), and 6 hours (±30 min) post-MLN0128 dose
- Fasting blood glucose at 0.5 hour (±15 min)
- Dispense MLN0128 and provide dosing instructions to the subject.

10.2.2.3 Cycle 2 Weeks 2 and 3 (Cycle 2 Days 8±1 and 15±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Weight, vital signs and ECOG performance status (see Appendix A)
- Symptom directed physical examination
- Laboratory assessments
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycle 2 Days 8±1 and 15±1)

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7 and LFTs are acceptable
- Administration of trastuzumab and paclitaxel, respectively, for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Cycle 2 Days 9±1 and 16±1)

- Administer MLN0128 approximately 24 hours following paclitaxel infusion.

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.2.4 Cycle 2 Week 4 (Cycle 2 Day 22±1)

Assessments prior to MLN0128 dosing for subjects receiving MLN0128P or prior to trastuzumab dosing for subjects receiving MLN0128PH (note, subjects will not receive paclitaxel or trastuzumab at this visit):

- Weight, vital signs and ECOG performance status (see Appendix A)
- Symptom directed physical examination
- Laboratory assessments
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting glucose (electrolyte levels should be corrected as needed prior to MLN0128 dosing)
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)
- Administration of trastuzumab for subjects receiving MLN0128PH

MLN0128 Administration

- Administer MLN0128 (after completion of trastuzumab infusion for subjects receiving MLN0128PH)

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.3 Cycle 3 and Cycle 4

10.2.3.1 Cycles 3 and 4 Week 1 (Cycles 3 and 4 Day 1±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Complete physical examination including weight, vital signs and ECOG performance status (see Appendix A)
- Tumor radiological assessments (prior to C3D1): CT (with contrast) or MRI scans of chest, abdomen, and/or pelvis should be performed approximately after 2 cycles of therapy within 7 days prior to C3D1. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of ≥ PR. The method (CT or MRI) used to assess tumor response in a subject must be the same throughout the study
- C3D1: Tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA)
- C4D1 (±7days): ECHO/MUGA for subjects receiving MLN0128PH only
- Laboratory assessments
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and overnight fasting glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
    - PTT and PT/INR
    - HbA1c (should be performed on Day 1 every 3 months starting C4D1)
    - Fasting serum lipid profile: total cholesterol, HDL-C, LDL-C, triglycerides
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Day 1 of Cycles 3 and 4):

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7, LFTs, and PT/INR and PTT are acceptable

- Administration of trastuzumab and paclitaxel, respectively, for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Day 2 of Cycles 3 and 4):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion.

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.3.2 Cycles 3 and 4 Week 2 (Cycles 3 and 4 Day 8±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Weight, vital signs and ECOG performance status (see Appendix A)
- Symptom directed physical examination
- Laboratory assessments
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting serum glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycles 3 & 4 Day 8±1):

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7 and LFTs are acceptable
- Administration of trastuzumab and paclitaxel, respectively, for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Cycles 3 & 4 Day 9±1):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion.

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.3.3 Cycles 3 and 4 Week 3 (Cycles 3 and 4 Day 15±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Weight, vital signs and ECOG performance status (see Appendix A)
- Symptom directed physical examination
- Laboratory assessments
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and overnight fasting glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycles 3 & 4 Day 15±1):

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7 and LFTs are acceptable
- Administration of trastuzumab and paclitaxel respectively for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Cycles 3 & 4 Day 16±1):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.3.4 Cycles 3 and 4 Week 4 (Cycles 3 and 4 Day 22±1)

Assessments prior to MLN0128 dosing alone for subjects receiving MLN0128P or prior to trastuzumab dosing for subjects receiving MLN0128PH (note, subjects will not receive paclitaxel at this visit):

- Symptom directed physical examination including weight, vital signs and ECOG performance status (see Appendix A)
- Laboratory assessments
    - Hematology: CBC with differential, hematocrit, platelet count, and hemoglobin
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting glucose (electrolyte levels should be corrected as needed prior to MLN0128 or trastuzumab dosing)
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Assessments of adverse events including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)
- Administration of trastuzumab for subjects receiving MLN0128PH

MLN0128 Administration

Administer MLN0128 (after completion of trastuzumab infusion for subjects receiving MLN0128PH).

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.4 Cycle 5 and Onward

10.2.4.1 Cycle 5 and Onward Week 1 (Cycle 5 and onward Day 1±1

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Complete physical examination including weight, vital signs and ECOG performance status (see Appendix A)

- Laboratory assessments
  - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
  - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and overnight fasting glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
  - Coagulation: PTT and PT/INR
  - Fasting serum lipid profile: total cholesterol, HDL-C, LDL-C, triglycerides
  - HbA1c
  - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Tumor radiological assessments: CT (with contrast) or MRI scans of chest, abdomen and/or pelvis should be performed for response assessment approximately every 2 cycles (±7 days) starting from C3D1. A confirmatory scan should be performed approximately 4 weeks from the previous scan for all subjects with an objective response of ≥ PR. The method (CT or MRI) used to assess tumor response in a subject must be the same throughout the study
- Tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA) should also be performed approximately every 2 cycles (±7 days) starting from C3D1
- ECHO/MUGA every 3 cycles (±7 days) starting from Cycle 4 Week 1 for subjects receiving MLN0128PH only
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycle 5 and onward Day 1):

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7 and LFTs are acceptable
- Administration of trastuzumab and paclitaxel, respectively, for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Cycle 5 and onward Day 2):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.4.2 Cycle 5 and Onward Week 2 (Cycle 5 and Onward Day 8±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Weight, vital signs and ECOG performance status (see Appendix A)
- Symptom directed physical examination
- Laboratory assessments
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting serum glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycle 5 and onward Day 8±1):

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7 and LFTs are acceptable
- Administration of trastuzumab and paclitaxel, respectively, for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Cycle 5 and onward Day 9±1):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.4.3 Cycle 5 and Onward Week 3 (Cycle 5 and Onward Day 15±1)

Assessments prior to paclitaxel dosing for subjects receiving MLN0128P or trastuzumab dosing for subjects receiving MLN0128PH:

- Weight, vital signs and ECOG performance status (see Appendix A)
- Symptom directed physical examination

- Laboratory assessments
  - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
  - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting serum glucose (electrolyte levels should be corrected as needed prior to paclitaxel or trastuzumab dosing)
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Paclitaxel and Trastuzumab Administration (Cycle 5 and onward Day 15±1):

- Administration of paclitaxel for subjects receiving MLN0128P if results of CBC, CHEM-7 and LFTs are acceptable
- Administration of trastuzumab and paclitaxel, respectively, for subjects receiving MLN0128PH if results of CBC, CHEM-7 and LFTs are acceptable

MLN0128 Administration (Cycle 5 and onward Day 16±1):

- Administer MLN0128 approximately 24 hours following paclitaxel infusion

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.2.4.4 Cycle 5 onward Week 4 (Cycle 5 onward Day 22±1)

Please note this clinic visit is only required for subjects receiving MLN0128PH

Assessments prior to trastuzumab dosing for subjects receiving MLN0128PH (note, subjects will not receive paclitaxel at this visit):

- Weight, vital signs and ECOG performance status (see Appendix A)
- Symptom directed physical examination
- Laboratory assessments
  - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
  - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and fasting serum glucose (electrolyte levels should be corrected as needed prior to trastuzumab dosing)
- Assessments of AEs including a review of the daily FBG readings from the glucometer
- Concomitant medications

- Conduct drug accountability on the returned empty bottles and unused medications. Compliance of the dosing will be monitored and documented (see Section 7.5.11)

Prior to MLN0128 dosing:

- Administration of trastuzumab

MLN0128 Administration:

Administer MLN0128 after completion of trastuzumab infusion for subjects receiving MLN0128PH

Procedure(s) after MLN0128 dosing:

- Return the glucometer to the subject for continued daily fasting glucose monitoring
- Dispense MLN0128 and provide dosing instructions to the subject

10.3 Termination Visit

The following assessments must occur within 30 days after the last administration of MLN0128, paclitaxel, or trastuzumab, whichever is discontinued last:

- Complete physical examination including weight, vital signs and ECOG performance status (see Appendix A)
- 12 -lead ECG (see Section 7.8.2.1)
- Laboratory assessments
    - Hematology: CBC with differential, hemoglobin, hematocrit, and platelet count
    - HbA1c
    - Chemistry (fasting): BUN, creatinine, ALT, AST, alkaline phosphatase, LDH, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium and overnight fasting glucose
    - Coagulation: PTT and PT/INR
    - Fasting serum lipid profile: total cholesterol, HDL-C, LDL-C, triglycerides
    - Urinalysis: macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (record levels as available) and microscopic analysis if an abnormality is noted. Microscopic urinalysis will also be performed along with a 12-hour urine collection and spot urine electrolytes, protein and creatinine and serum chemistry at any time when the serum creatinine is ≥ Grade 1 according to NCI CTCAE version 4.0.
- Tumor radiological assessments and tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA) for subjects who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks: CT (with contrast) or MRI scans of chest, abdomen and pelvis. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of ≥ PR. The method (CT or MRI) used to assess tumor response in a subject must be the same throughout the study

- ECHO/MUGA for subjects receiving MLN0128PH only
- Assessments of AEs
- Concomitant medications
- Conduct drug accountability on the returned empty bottles and unused medications

11 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section outlines the statistical analysis strategy and procedures for the study. Specific details of the primary and key secondary analyses will be provided in the Statistical Analysis Plan (SAP). If, after the study has begun, but prior to the final analysis, important changes are made to the protocol that affect principal features of the primary or key secondary analyses, then the protocol and/or SAP will be amended, as appropriate. Any other changes made to the planned analyses after the protocol and SAP have been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

11.1 Analysis Endpoints

The safety and efficacy endpoints to be evaluated are listed below, followed by descriptions of the derivations of selected endpoints.

11.1.1 Primary Endpoints

11.1.1.1 Dose Escalation Phase:

The maximum tolerated dose of MLN0128 will be determined when administered orally QDx3d QW and/or via alternate dosing schedules (such as QDx5d QW) in combination with weekly paclitaxel in subjects with advanced solid malignancies. The MTD of each dosing schedule is defined as the highest dose level of MLN0128 administered at which no more than 1 out of 6 evaluable subjecting experiencing DLT during the first treatment cycle. The rate of DLT will be determined from the occurrence of adverse events which meet the criteria in Section 7.2.1.

11.1.1.2 Expansion Phase:

The objective response rate will be estimated for each tumor histology cohort studied in the expansion phase. Arm A will consist of HER2– cancer subjects receiving MLN0128P; Arm B will consist of HER+ cancer subjects receiving MLN0128P plus weekly trastuzumab (MLN0128PH). The objective response rate will be based on the subject's best overall tumor response documented during the course of protocol therapy. Objective response includes CR and PR and will be determined based on RECIST (version 1.1). The duration of objective response will be evaluated for subjects who achieve CR or PR.

11.1.2 Secondary Endpoints

The plasma pharmacokinetics of MLN0128 in combination with paclitaxel will be determined from selected subjects based on the PK parameters listed below. The plasma pharmacokinetics of paclitaxel in combination with MLN0128 will be evaluated in a similar manner. Plasma samples for PK analysis will be collected at the times specified in the Schedule of Events.

- Maximum plasma concentration (C_{max})

- Minimum plasma concentration (C_{min})
- Time of maximum plasma concentration (T_{max})
- Plasma half-life ($t_{½}$)
- Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), zero to last dose (AUC_{0-last}), and %AUC extrapolated
- The additional intravenous PK parameters, CL, and V_{ss} will be estimated for paclitaxel

11.1.3 Safety and Tolerability Endpoints

Safety and tolerability of MLN0128P and MLN0128PH will be assessed in each study phase (if applicable) based on the following:

- Incidence, duration, and severity of treatment-emergent adverse events, including dose-limiting toxicity (see Section 7.2.1), serious adverse events, adverse events resulting in permanent discontinuation of protocol treatment, and deaths within 30-days of the last dose of protocol treatment
- Changes in laboratory test results including chemistry and hematology
- Changes in vital signs including blood pressure, pulse, and temperature
- Changes in electrocardiogram results

11.2 Analysis Populations

11.2.1 Safety Analysis

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 at least 1 dose of MLN0128. The safety data from the dose escalation phase will be summarized by dose cohort; and by tumor histology cohort for the expansion phase.

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

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study drug is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

11.2.2 Efficacy Analysis

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 for 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 study drug
- Lack of baseline data for those analyses that require baseline data

Subjects will be grouped in the FAS population according to tumor histology. A supportive analysis using the Per-Protocol population will be performed for the tumor response analysis. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary analysis. The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made prior to locking the clinical database and final analysis and will be documented in a separate memo.

11.3 Statistical Methods

11.3.1 Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, DLTs, laboratory values, electrocardiogram results, and vital signs.

The observed DLT rate will be calculated by the crude proportion of subjects who experience DLT during the first cycle of protocol treatment. Multiple concurrent adverse events leading to DLT will be considered a single DLT. The estimate of the DLT rate will be accompanied by a 2-sided 95% exact binomial confidence interval. The relationship between the dose of MLN0128 and probability of DLT will be assessed by fitting various regression models such as E_{max}, logistic and exponential model shapes.

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as adverse events that start on or after the first administration of protocol treatment and within 30 days of the last administration. Adverse events will be summarized by the number and percentage of subjects who experienced the event, according to system organ class and preferred term. A subject reporting multiple cases of the same adverse event will be counted once within each system organ class and similarly counted once within each preferred term. Unless specified otherwise, the denominator for these calculations will be based on the number of subjects in each dose cohort who receive at least 1 administration of MLN0128, irrespective of the total number of doses or treatment cycles administered. These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered. AE incidence rates may also be calculated based on other measures of subject exposure (eg, total

number of treatment cycles administered). AEs will also be summarized by NCI-CTCAE version 4.0 severity, grade, and by relationship to each treatment administered. Additional summaries may also be provided for SAEs, and events resulting in the permanent discontinuation of protocol therapy. All AEs will be included in individual subject listings.

The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled and unscheduled protocol assessment time point. Changes will be calculated relative to the values collected at baseline and on the first day of each cycle of treatment. The incidence of grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided by treatment cycle and across all treatment cycles. The toxicity grades for laboratory tests will be based on NCI-CTCAE version 4.0 criteria. The use of blood transfusions (platelets, red blood cells) and/or growth factor support will be reported. Similar analyses will be done for selected chemistry tests (including liver and renal function tests). Subject listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in the subject listings and will include flags for high and low values.

Vital sign results (blood pressure, pulse, respirations, and temperature) will be summarized descriptively for each scheduled and unscheduled protocol time point. Changes will be calculated relative to the assessments at baseline and on the first day of each cycle of therapy.

11.3.2 Efficacy Analysis

The efficacy analysis will be conducted for the FAS and Per-Protocol populations defined in Section 11.2.2. The results of this analysis will be presented by tumor histology cohort.

Objective Response Rate:
The objective response rate will be estimated for each tumor histology cohort in the expansion phase. The estimate of the objective response rate will be calculated based on the maximum likelihood estimator (ie, crude proportion of subjects whose best overall response is CR or PR). The estimate of the objective response rate will be accompanied by 1-sided and 2-sided 95% exact binomial confidence intervals.

Duration of Objective Response:
The duration of objective response will be calculated for subjects who achieve CR or PR. For such subjects, the duration of objective response is defined as the number of days from the start date of PR or CR (whichever response is achieved first) to the first date that progressive disease is objectively documented. Disease progression will be determined by the Investigator using RECIST (version 1.1). The duration of objective response will be right-censored for subjects who achieve CR or PR and meet 1 of the following conditions: 1) non-protocol anticancer treatment started before documentation of disease progression, 2) death or documented disease

progression after more than 1 missed disease assessment visit, or 3) alive and does not have documentation of disease progression before a data analysis cutoff date. For such subjects, the duration of objective response will be right-censored according to Table 11.1 below. These conventions are based on the May 2007 FDA Guidance for Industry, '*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*' (fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf).

The duration of objective response will be summarized descriptively using the Kaplan-Meier method. The 50th percentile of the Kaplan-Meier distribution will be used to estimate the median response duration.

Table 11.1 Date of Progression or Censoring for Duration of Response

Situation	Date of Progression or Censoring	Outcome
Non-protocol anti-cancer treatment started before death or documentation of disease progression or death	Date of last disease assessment prior to start of non-protocol anticancer treatment	Censored
Death or progression after more than 1 missed disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the first missed visit	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

11.4 Sample Size Determination

11.4.1 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.

11.4.2 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 30 HER2– cancer subjects receiving MLN0128P
- Arm B will consist of approximately 30 HER2+ cancer subjects receiving MLN0128PH. Up to 3 subjects will be enrolled initially in Arm B and observed for one cycle prior to enrolling additional subjects into this arm.

The approximate sample size of 30 subjects in Arms A and B is based on following considerations: An experimental regimen 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 15% or greater is considered sufficient to warrant further study of the regimen. Up to 30 subjects in each arm will provide greater than 90% 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%.

11.5 Interim Analysis and Early Stopping Guidelines

Safety will be monitored throughout the trial. Dose escalation will proceed according to the dose escalation scheme described in Section 7.2.3. If any significant safety issues arise, the Sponsor will be notified and if necessary, a decision to modify or terminate the trial (or 1 of the cohorts) will be made.

All participating sites are required to provide DLT notification forms within 24 hours of learning of the event. Additionally, site teleconferences between the Sponsor and all participating sites will be held approximately every 1 to 2 weeks during the dose escalation phase to discuss any suspected AEs/DLTs that have occurred at each cohort. Participating Investigators and the Sponsor's Medical Monitor will review study drug-related toxicities from the current cohort during the site teleconferences before initiating enrollment into the next planned dose cohort.

11.6 Changes in the Conduct of the Study or Planned Analyses

Only Millennium may modify the protocol. Any change in study conduct considered necessary by the PI will be made only after consultation with Millennium, who will then issue a formal protocol amendment to implement the change. The only exception is when an Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/EC must be sought, and the Investigator should inform Millennium and the full IRB/EC within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/EC must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/EC prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by Millennium and the IRB/EC, and all active subjects must again provide informed consent.

12 ETHICS

12.1 Institutional Review Board or Ethics Committee

Prior to initiating the study, the Investigator will obtain written confirmation that the Institutional Review Board (IRB) is properly constituted and compliant with all United States Food and Drug Administration (FDA) requirements and local regulations. A copy of the confirmation from the IRB/EC will be provided to Millennium or its designee. The Principal Investigator (PI) will provide the IRB/EC with all appropriate material, including the protocol, Investigator's Brochure, the Informed Consent Form (ICF), and any other written information provided to the subjects, including all consent forms translated to a language other than the native language of the clinical site. The study will not be initiated until appropriate IRB approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the PI and copies are received at Millennium or its designee. The approval document should refer to the study by protocol title and Millennium, protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. Appropriate reports on the progress of the study should be made to the IRB/EC or REB and Millennium or its designee by the PI in accordance with applicable governmental regulations and in agreement with policy established by the IRB/EC and Millennium.

12.2 Ethical Conduct of Study

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject, or his/her legally authorized representative will provide written, informed consent before any study-related tests or evaluations are performed.

12.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with the Declaration of Helsinki, ICH GCP and US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25 [a,b.], CFR 50.27, and CFR Part 56, Subpart A), HIPAA for the US only, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and HIPAA authorization and provide the documents to Millennium or its designee for approval prior to submission to the IRB. Millennium and the IRB/EC must approve the documents before they are implemented. If a subject is unable to sign the ICF and HIPAA authorization, a legal representative may sign for the subject. The

Investigator will provide copies of the signed ICF to each subject (or the subject's legal representative) and will maintain the original in the subject's record file.

13 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the PI at each site must provide to Millennium or its designee a fully executed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of research subjects in this study.

The study will be administered by and monitored by employees or representatives of Millennium. CRAs will monitor each site on a periodic basis and perform verification of source documentation for each subject as well as other required review processes. Millennium's designee will be responsible for the timely reporting of SAEs to appropriate regulatory authorities as required.

14 CASE REPORT FORMS AND SOURCE DOCUMENTS

CRF data will be entered electronically for this study. Millennium's policy is that study data on the CRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). A CRA designated by Millennium will compare the eCRFs with the original source documents at the study site and evaluate the CRFs for completeness and accuracy. Designated site personnel must complete the eCRFs as soon as possible after a subject visit, and the forms must be available for review at the next scheduled monitoring visit. The Investigator must review and sign off on the completed eCRFs to verify their accuracy.

15 STUDY MONITORING AND AUDITING

Qualified individuals designated by Millennium will monitor all aspects of the study according to GCP and standard operating procedures for compliance with applicable government regulations. The PI agrees to allow these Millennium-designated CRAs direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records, of the study subjects, and, if requested, agrees to assist the Millennium-designated CRAs. The PI and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by Millennium or its designees.

Members of Millennium GCP Compliance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The PI will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an audit of the study. If informed of such an inspection, the PI should notify Millennium immediately. The PI will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

16 RETENTION OF RECORDS

The PI must retain all study records required by Millennium and by the applicable regulations in a secure and safe facility. The PI must notify Millennium of any change in the location, disposition or custody of the study files. The PI/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (eg, subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the U.S. or an ICH region and until (1) there are no pending or contemplated marketing applications in the U.S. or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. No records relating to this study should be disposed of without the written approval of Millennium. It is the responsibility of Millennium to inform the PI/institution as to when these documents no longer need to be retained.

17 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Millennium and the IRB for each study site, if appropriate.

18 REFERENCES

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12. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

19 PROTOCOL ACCEPTANCE PAGE

Study 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
Protocol Number:	INK128-003
Investigational Product:	MLN0128 (formerly INK128)
Sponsor:	Millennium Pharmaceuticals, Inc. 40 Landsdowne Street Cambridge, MA USA 02139
Medical Monitor:	PPD
Original Protocol Date:	January 12, 2011
Amendment 1 Date:	July 15, 2011
Amendment 2 Date:	October 12, 2011
Amendment 3 Date:	April 03, 2012
Amendment 4 Date:	May 21, 2012
Amendment 5 Date:	July 30, 2012
Amendment 6 Date:	March 25, 2013
Amendment 7 Date:	March 5, 2014

By my signature below, I hereby state that I have read, and agree to abide by, the instructions, conditions, and restrictions of the protocol referenced above.

_____ _____

Investigator Signature Date

_____

Printed Name of Investigator

Please return the signed form to Millennium or its designee. Contact details will be provided to the Investigator. Please retain a copy for your study files.

20 APPENDICES

20.1 Appendix A: ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

20.2 Appendix B: A LIST OF STRONG CYP3A4, CYP2C9 AND CYP2C19 INDUCERS/INHIBITORS

ganfyd.org/index.php?title=Inhibitors_of_CYP3A4

medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp

Strong Inhibitors

Drugs	**Fruits and Fruit Juices**
indinavir	Star fruit & star fruit juice
nelfinavir	Pomegranates & pomegranate juice
ritonavir	Papaya & papaya juice
clarithromycin	Grapefruit & grapefruit juice
itraconazole	Seville oranges & seville orange juice
ketoconazole	
nefazodone	
fluconazole	
saquinavir	
telithromycin	

Inducers

carbamazepine

phenobarbitol

phenytoin

rifabutin

St. John's wort

troglitazone

secobarbitol

rifampin

20.3 Appendix C New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

20.4 Appendix D: Amendment 7 Summary of Changes

THE PRIMARY SECTION(S) OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 7 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Replace PPD s the global clinical lead

The primary change occurs on the cover page:

Formerly read:	Sponsor's Responsible Medical Officer	PPD
Now reads:	Sponsor's Responsible Medical Officer	PPD

Sections that also contain this change are:

- Protocol Approval Page
- Section 19, PROTOCOL ACCEPTANCE PAGE

Purpose: Align the AE collection period in the Schedule of Events with Section 8.3, Monitoring of Adverse Events and Period of Observation, by removing reference to the collection of AEs before initiation of new anticancer therapy

The primary change occurs in the Schedule of Events, Table 2.1, Schedule of Events – Cycle 1:

Deleted text:	15. Adverse events will be collected after administration of the first dose of MLN0128, paclitaxel or trastuzumab through 30 days following the last dose of study drug ~~or initiation of new anti-cancer therapy, whichever comes first~~.

Purpose: Extend the period of contraception duration from 30 days to 90 days after the last dose of study drug based on teratogenic and abortive effects identified during preclinical embryofetal studies in rats

The primary change occurs in Section 7.4.1, Inclusion Criteria:

Formerly read:	9. For women of child-bearing potential, negative serum pregnancy test within 14 days prior to the first study drug administration and use of physician-approved method of birth control from 30 days prior to the first study drug administration to ~~30~~ days following the last study drug administration; 10. Male subjects must be surgically sterile or must agree to use physician-approved contraception during the study and for ~~30~~ days following the last

	study drug administration;
Now reads:	9. For women of child-bearing potential, negative serum pregnancy test within 14 days prior to the first study drug administration and use of physician-approved method of birth control from 30 days prior to the first study drug administration to **90** days following the last study drug administration; 10. Male subjects must be surgically sterile or must agree to use physician-approved contraception during the study and for **90** days following the last study drug administration;

Section 2, Synopsis, also contains this change.

Purpose: Update SAE reporting information to align with current procedures

The primary change occurs Section 8.2, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:	SAE Reporting Contact Information ~~– United States and Canada~~ ~~PPDI Pharmacovigilance~~ ~~Fax: 888-488-9697~~ ~~24-hour helpline: 800-201-8725~~ ~~SAE Reporting Contact Information – Rest of World (except Central and South America)~~ ~~PPDI Pharmacovigilance~~ ~~Fax: +44 1223 374102~~ ~~24-hour helpline: +44(0)1223 374240~~
Now reads:	SAE Reporting Contact Information **Cognizant** **United States and Canada** **Toll-Free Fax #: 1-800-963-6290** **Email: TakedaOncoCases@cognizant.com** **All Other Countries (Rest of World)** **Fax #: 1-202-315-3560** **Email: TakedaOncoCases@cognizant.com**

Purpose: Correct typographical errors, grammar, punctuation, and formatting

These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical Approval	05-Mar-2014 18:48
	Clinical Approval	06-Mar-2014 14:20