



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

NCT Number: NCT01058707

Protocol Approve Date: January 17, 2018

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

**MLN0128**

**Clinical Study Protocol INK128-001 Amendment 20, EudraCT: 2009-017284-42**

## **1. CLINICAL STUDY PROTOCOL**

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

**Protocol Number:** INK128-001

**Investigational Product** MLN0128 (also known as TAK-228 and INK128)

**US IND Number** 104,801

**EudraCT Number** 2009-017284-42

**Indication** Advanced Malignancies

**Sponsor** Millennium Pharmaceuticals, Inc.  
40 Landsdowne Street, Cambridge, MA USA 02139

**Development Phase** Phase 1  
PPD

**Sponsor's Responsible Medical Officer** Global Clinical Lead

**Original Protocol Date:** November 3, 2009

**Amendment 1 Date:** December 3, 2009

**Amendment 2 Date:** January 28, 2010

**Amendment 3 Date:** March 31, 2010

**Amendment 4 Date:** July 20, 2010 (not implemented)

**Amendment 5 Date:** August 12, 2010

**Amendment 6 Date:** September 14, 2010

**Amendment 7 Date:** October 27, 2010

**Amendment 8 Date:** December 21, 2010

**Amendment 9 Date:** March 25, 2011

**Amendment 10 Date:** June 28, 2011

**Amendment 11 Date:** October 12, 2011

**Amendment 12 Date:** April 03, 2012

**Amendment 13 Date:** May 21, 2012

**Amendment 14 Date:** July 30, 2012

**Amendment 15 Date:** March 27, 2013

**Amendment 16 Date:** July 3, 2013

**Amendment 17 Date:** March 5, 2014

**Amendment 18 Date:** September 26, 2016

**Amendment 19 Date:** November 28, 2017

**Amendment 20 Date:** January 17, 2018

Note: This document was approved electronically; the electronic approval signatures can be found at the end of the document.

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### **Rationale for Amendment 20**

This document describes the changes to the protocol incorporating Amendment 20. The primary purpose of this amendment is to provide consistency within the protocol that no dietary restrictions will be imposed on study subjects.

### **Purposes for Amendment 20**

1. Remove dietary restrictions related to CYP inhibitors and inducers consistently within the protocol.
2. Revise the list of CYP inhibitors and inducers regarding concomitant medications.
3. Update the FDA guidance link.

For specific examples of changes in text and where the changes are located, see Section [21.4](#).

**MLN0128**

**Clinical Study Protocol INK128-001 Amendment 20, EudraCT: 2009-017284-42**

## **2. PROTOCOL APPROVAL PAGE**

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

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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. Electronic signatures appear at the end of this document.

PPD

### 3. SYNOPSIS

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

**Protocol Number:** INK128-001

**Study Sites:** Multiple centers in the United States (US) and Spain

**Study Period (months):** Approximately 32 months

**Phase of Development:** Phase I

#### Study Objectives

##### Primary

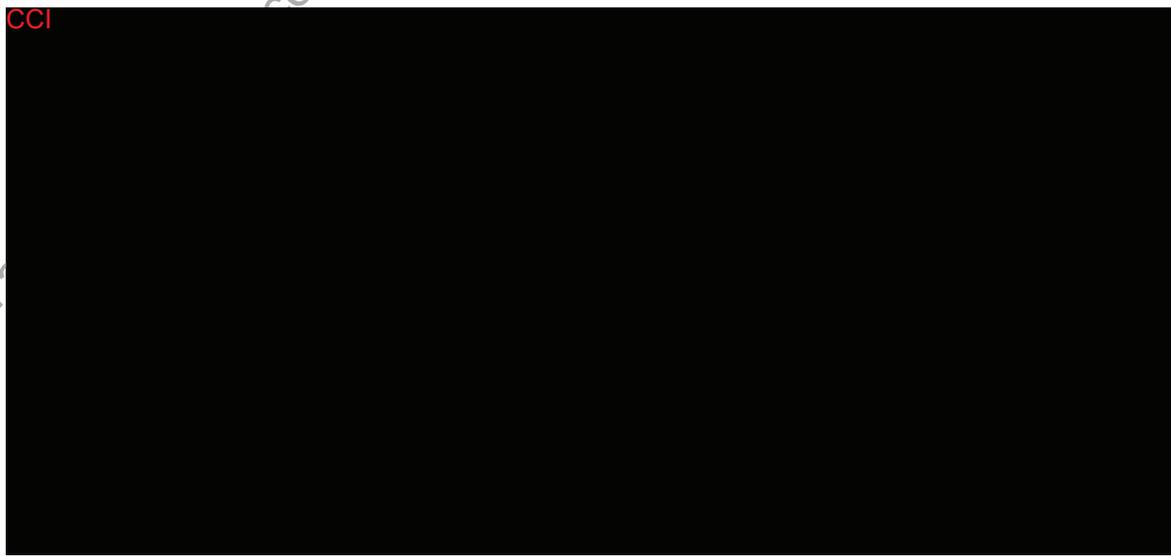
- To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of oral administration of MLN0128 (also known as TAK-228 and INK128) given daily or via alternate dosing schedules in subjects with advanced malignancies
- To evaluate the safety and tolerability of orally administered single-agent MLN0128, given daily or via alternate dosing schedules, in both the dose escalation and the expansion phases of the study

##### Secondary

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

##### Exploratory

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**Overview of Study Design:** This is a phase 1, open-label study that consists of a dose escalation phase in subjects with advanced malignancies, followed by an expansion phase of safety and efficacy in up to 80 additional response-evaluable subjects with measurable disease in 2 dosing schedules in 2 tumor-specific cohorts.

Up to 4 different dosing schedules will be explored in the dose escalation phase: once daily (QD), once weekly (QW), once daily for 3 days on, 4 days off repeated each week (QD×3d QW), and once daily for 5 days on, 2 days off repeated each week (QD×5d QW). Enrollment will start with the once daily schedule. Once the MTD for this schedule is identified, enrollment will begin in parallel in the alternate dosing schedules. Once the MTD has been identified for each of the 4 dosing schedules evaluated, an additional 6 subjects may be enrolled in 1 or more of the dosing schedule(s) to gain further PK and safety data to determine the recommended dose(s) and schedule(s) prior to the expansion phase of the study.

Based on biochemical data, available PK, and tolerability data for each MLN0128 dosing schedule, along with potential early signs of anti-tumor activity from subjects treated during the dose escalation phase, 1 or more dosing schedules will be evaluated for safety and efficacy, in parallel, in the expansion phase. A total of up to 80 response-evaluable subjects will comprise 2 tumor-specific cohorts: an RCC cohort and a cohort of selected tumor types (endometrial and bladder cancers).

**Number of subjects planned:** Dose escalation phase – approximately 90 subjects; Expansion phase – approximately 80 response-evaluable subjects

**Diagnosis and All Criteria for Inclusion and Exclusion**

*Individuals eligible to participate in either the dose escalation phase and/or the expansion phase of the study must meet all of the following Inclusion Criteria:*

1. Age  $\geq$  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 standard-of-care therapy. Subjects with locally advanced or metastatic solid tumors who have 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, they 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. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1;
4. Subjects must have adequate organ function, including the following:
  - a. Bone marrow reserve consistent with: absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$ ; platelet count  $\geq 100 \times 10^9/L$ ; hemoglobin  $\geq 9$  g/dL;
  - b. Hepatic: total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT)  $\leq 2.5 \times$  ULN ( $\leq 5 \times$  ULN if liver metastases are present);
  - c. Renal: creatinine clearance  $\geq 50$  mL/min based either on Cockcroft-Gault estimate or based on urine collection (12 or 24 hour);
  - d. Metabolic: fasting serum glucose ( $\leq 130$  mg/dL) and fasting triglycerides  $\leq 300$  mg/dL;
5. Left ventricular ejection fraction (LVEF) within 5 absolute percentage points of 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);

6. 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;
7. 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;
8. Willingness to provide paraffin blocks or a minimum of 10 unstained slides of available archival tumor tissues (paraffin blocks are preferred);
9. Ability to swallow oral medications;
10. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures;

Subjects who have tumor tissue that is accessible for biopsy based on the investigator's judgment will be strongly encouraged to consent for tumor biopsy.

*Additionally, for individuals eligible to participate in the expansion phase of the study:*

11. Subjects must have evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1<sup>(1)</sup> by radiographic techniques (computerized tomography [CT] or magnetic resonance imaging [MRI]);
12. Subjects must have a pathologic diagnosis of advanced or recurrent endometrial adenocarcinoma, and must have failed at least 1 prior line of standard chemotherapy; or
13. Subjects must have a pathologic diagnosis of advanced/metastatic urothelial cancer (carcinoma of the bladder, ureter, and/or renal pelvis) and must have failed at least 1 line of prior therapy in the metastatic/unresectable setting; or
14. Subjects must have a pathologic diagnosis of advanced renal cell carcinoma (RCC) and must have failed at least 1 prior line of anti-VEGF therapy (including but not limited to sunitinib, and/or sorafenib, and/or bevacizumab and/or pazopanib, and/or axitinib) and must not have received prior therapy with a TORC1 inhibitor (such as temsirolimus or everolimus); or
15. Subjects must have a pathologic diagnosis of advanced renal cell carcinoma (RCC) and must have progressed on previous treatment with a TORC1 inhibitor (such as temsirolimus or everolimus).

*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. Untreated brain metastasis or history of leptomeningeal disease or spinal cord compression;
3. Failed to recover from the reversible effects of prior anticancer therapies with the exception of alopecia, and after-effects associated with prior tyrosine kinase inhibitor therapy, such as hair depigmentation, hypothyroidism, and/or splinter hemorrhage;
4. 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 equal 28 days prior to the first administration of study drug, and the subject

- must have documented disease progression;
5. Have received systemic corticosteroid (inhalers are allowed) within 1 week prior to the first administration of study drug (dose escalation phase only);
  6. Have initiated treatment with bisphosphonates less than 30 days prior to the first administration of MLN0128. Concurrent bisphosphonate use is only allowed if the bisphosphonate was initiated at least 30 days prior to the first administration of MLN0128;
  7. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128;
  8. 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;
  9. Other clinically significant comorbidities, such as uncontrolled pulmonary disease, active CNS disease, active infection, or any other condition that could compromise subject's participation in the study;
  10. Known human immunodeficiency virus (HIV) infection;
  11. Pregnancy (positive serum or urine pregnancy test) or breast feeding;
  12. Any history of unstable angina, myocardial infarction, New York Heart Association (NYHA) Class III or IV heart failure (See [Table 21-3](#)), and/or pulmonary hypertension;
  13. Significant active cardiovascular disease including:
    - Uncontrolled high blood pressure (ie, systolic blood pressure > 180 mmHg, diastolic blood pressure > 95 mmHg)
    - Grade 3 or higher valvular disease
    - Grade 3 or higher atrial fibrillation
    - Grade 3 or higher bradycardia
    - Endocarditis
    - Pulmonary embolism
    - Recent cerebrovascular accident/transient ischemic attack within 6 months prior to enrollment
  14. A requirement for positive inotropic support (excluding digoxin) or active/serious uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation) within 1 year prior to screening;
  15. A pacemaker or implantable cardiac defibrillator;
  16. Baseline prolongation of the rate-corrected QT interval (QTc) (eg, repeated demonstration of QTc interval > 480 milliseconds; See Section [8.6.7.3](#));
  17. History of congenital long QT syndrome, ventricular fibrillation, ventricular tachycardia, or torsades de pointes;
  18. Diagnosed or treated for another malignancy within 2 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection;

19. Additionally, for individuals eligible to participate in the expansion phase of the study, subjects will be excluded if they have received prior AKT, PI3K, dual PI3K/mTOR complex (TORC1/2), or TORC1/2 inhibitors.

Other considerations for exclusion: Subjects taking moderate/strong CYP1A2 inhibitors, moderate CYP1A2 and/or strong and moderate CYP3A4 inducers should be considered with caution. Alternative treatments that are less likely to affect MLN0128 metabolism, if available, should be considered. If a subject requires treatment with 1 or more moderate/strong CYP1A2 inhibitor, a moderate/strong CYP1A2 and/or a strong CYP3A4 inducer, the medical monitor should be consulted. Examples of clinically relevant moderate/strong CYP1A2 inhibitors and inducers, as well as strong CYP3A4 inducers, are presented in Table 21.2.

#### Investigational Product(s), Dose, Route, and Regimen

MLN0128 (also known as TAK-228 and INK128) is supplied in tamper-resistant, high-density polyethylene bottles as capsules containing 1-, 3-, or 5-mg dose strengths, which the pharmacist will use to make up the appropriate dose for each dose cohort. On clinic days only, subjects will be instructed not to take their study drug at home, and the site will administer MLN0128 to the subject from the bulk pharmacy supplies. The subject should take all the capsules orally for a given dose with a meal once in the morning for the QD, QW, QD×3d QW, and QD×5d QW dosing schedules. On each clinic day, the subject should return the study medication bottle and any unused study drug. A full accountability by the site staff and the sponsor's designated Clinical Research Associate (CRA) should be conducted before these supplies are destroyed.

Cycles occur in 28-day increments.

The starting dose for the QD dosing schedule is 2 mg QD. Dose escalation for the QD dosing schedule will be according to a modified Fibonacci schema. For example, the starting dose of 2 mg may be escalated in successive cohorts to 4 mg, 7 mg, 10 mg, 14 mg, 18 mg, etc. The investigators and sponsor, after their safety review, may elect to study a dose level that is intermediate to the current dose level and the next lower dose level previously studied, eg 6 mg as an intermediate dose between 4 mg and 7 mg. The level of dose escalation and a decision to go to an intermediate dose level will be determined after discussion between the participating investigators and Millennium's medical monitor before dose escalation, but will not exceed the planned dose according to a modified Fibonacci schema.

After the MTD has been determined for the once daily dosing schedule (MTD<sup>qd</sup>), study of the additional dosing schedules will begin. Enrollment will be initiated in parallel and independent arms: Arm A with once weekly (QW) dosing starting at a dose not to exceed twice the MTD<sup>qd</sup>; Arm B with MLN0128 administered once daily for 3 days on, 4 days off each week (QD×3d QW) starting at the MTD<sup>qd</sup>; and Arm C with MLN0128 administered once daily for 5 days on, 2 days off each week (QD×5d QW) starting at a dose not to exceed the total weekly dose of the MTD<sup>qd</sup> (eg, ≤ 42 mg). Subjects will be randomly assigned to 1 of the 3 alternate dosing arms in the event, that 2 or more arms are open for enrollment at the same time. Subjects may not participate in more than 1 dosing arm.

Dose escalation for each of the arms will be according to a modified Fibonacci schema. The extent of dose escalation will be determined after discussion between the participating investigators and Millennium's medical monitor prior to dose escalation, but will not exceed the planned dose according to a modified Fibonacci schema.

**Duration of Treatment:** In the absence of unacceptable MLN0128 treatment-related toxicity or disease progression, subjects may receive MLN0128 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.

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**Reference Therapy, Dose, Route, and Regimen:** None

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**Criteria for Evaluation**

**Safety:** Safety will be assessed by periodic physical examinations, 12-lead electrocardiograms (ECGs), 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 with each cohort. Participating investigators and the sponsor's medical monitor will review toxicities from the current cohort during the site teleconferences before escalating to the next dose level, expanding the cohort at the current dose level or exploring an intermediate dose level.

**Pharmacokinetics:** The PK profile will be assessed by determining the plasma levels of MLN0128 at intervals throughout the study. Blood samples for PK profile will be collected in subjects enrolled in the dose escalation phase of the study at the following time points:

- Cycle 1, Day 1 (C1D1): predose, 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min), 2 hours ( $\pm 30$  min), 4 hours ( $\pm 30$  min), 8 hours ( $\pm 30$  min) post-C1D1 dose;
- Cycle 1, Day 2 (C1D2 =  $24 \pm 2$  hours post-C1D1 dose): predose;
- Cycle 2, Day 1 (C2D1): predose, 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min), 2 hours ( $\pm 30$  min), 4 hours ( $\pm 30$  min), 8 hours ( $\pm 30$  min) post-C2D1 dose;
- Cycle 2, Day 2 (C2D2 =  $24 \pm 2$  hours post-C2D1 dose): predose

During the expansion phase, PK samples will be obtained according to the schedule provided in Table 3-5.

**Pharmacodynamics:** Throughout the study, pharmacodynamic assessment will be made by assessing various biomarker levels in samplings of peripheral blood cells (PBCs) (dose escalation phase only), skin and tumor biopsies pre- and posttreatment whenever possible. During dose escalation, the pharmacodynamic effect of MLN0128 activity in surrogate tissues (skin and tumor tissue) as measured by 4EBP1, AKT, and S6, as well as in peripheral blood cells via 4EBP1 will be evaluated. CCI

Blood samples for PBCs will be collected in all subjects at the following time points during the dose escalation phase of the study:

- Cycle 1, Day 1 (C1D1): predose, 2 hours ( $\pm 30$  min), 8 hours ( $\pm 30$  min) post-C1D1 dose, and
- Cycle 1, Day 2 (C1D2 =  $24 \pm 2$  hours post-C1D1 dose): predose, and
- Cycle 2, Day 1 (C2D1): predose, 2 hours ( $\pm 30$  min), 8 hours ( $\pm 30$  min) post-C2D1 dose, and
- Cycle 2, Day 2 (C2D2 =  $24 \pm 2$  hours post-C2D1 dose): pre-dose, and
- Termination visit

The previously mentioned biomarkers are downstream effectors of mTOR and have been used for determining the sensitivity of proliferative diseases to treatment with mTOR inhibitors. The changes in biomarkers levels will be determined via flow cytometry and/or immunohistochemical analysis. The absolute and percent change from baseline will be calculated for each subsequent measurement. Summary statistics will be computed for each collection time point.

*Predictive Markers of MLN0128 Activity:* Candidate somatic genetic markers that may predict MLN0128 activity will be evaluated in archival tumor tissues. These include phosphoinositide 3-kinase alpha catalytic subunit (PI3KCA), PTEN, and rat sarcoma (K/H/N) [Ras (K/H/N)] in archival paraffin tumor tissue with MLN0128 activity.

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**Efficacy:** Radiographic and/or physical assessments of the malignancy, and evaluations of relevant tumor markers (eg, cancer antigen 125 [CA125], prostate-specific antigen [PSA], cancer antigen 19-9 [CA19-9], cancer antigen 27.29 [CA27.29], cancer antigen 15.3 [CA15.3], and carcinoembryonic antigen [CEA]) will be made at screening/baseline (within 28 days prior to the first study drug administration) and after every 2 cycles of treatment (or at intervals of up to every 4 cycles for long-term patients [ie, study participation  $\geq 3$  years], as clinically indicated based on the investigator's judgment). 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 RECIST version 1.1. A confirmatory CT/MRI scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of  $\geq$  PR. The duration of stable disease will be evaluated for subjects with the best response of stable disease.

#### 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 phase will be summarized by dose cohort and schedule, and by tumor histology cohort for the expansion phase. For each study phase, the number and percentage of subjects experiencing 1 or more AEs will be summarized by the relationship to study drug and severity based on CTCAE v4.0. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Laboratory parameters will be summarized using descriptive statistics, by postdosing 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 and Pharmacodynamic Analyses:** Efficacy analyses will be conducted for the response-evaluable subjects enrolled in the expansion cohorts. The results of these analyses will be summarized for the renal cohorts. If there is a sufficient number of subjects with a specific tumor type, in the multi-tumor type cohort (ie, endometrial and bladder), then efficacy endpoints will also be summarized by tumor type. The number and percentage of subjects experiencing objective response (CR and PR) will be summarized. The duration of objective response will be summarized descriptively using the Kaplan-Meier method. For subjects with best response of stable disease, the duration of stable disease will be defined as the number of days from the date of first dose to the date of progressive disease. Summary statistics will be provided for the duration of MLN0128 therapy versus the duration of the last systemic anticancer therapy received on subjects whose last systemic anticancer therapy prior to entering the study was not an investigational agent. Summary statistics will be computed for baseline biomarkers. The absolute and percent change from baseline will be calculated for each subsequent measurement. Summary statistics will be computed for each collection time point.

**Pharmacokinetic Analyses:** Pharmacokinetic parameters, including area under the plasma concentration-time curve (AUC), maximum plasma concentration ( $C_{\max}$ ), minimum plasma concentration ( $C_{\min}$ ), time of maximum plasma concentration ( $T_{\max}$ ), and plasma half-life ( $t_{1/2}$ ) will be determined. Comparisons across dose levels will be made to assess proportionality. In addition, comparison between single-dose and multiple-dose PK parameters will be made for assessment of steady-state drug accumulation.

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**Schedule of Events****Schedule of Events for the Escalation Phase****Table 3-1 Schedule of Events – Escalation Phase, Cycle 1**

Assessments	Screening/Baseline		Treatment						Termination Visit (within 30 days of last dose)
	Within 28 days	Within 14 days	Day 1 (before dose)	Day 1	Day 2	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	
Informed Consent/PIC and HIPAA/DPA	X								
Medical History	X								
Vital signs, Height <sup>1</sup> , Weight and ECOG PS		X <sup>1</sup>	X <sup>14</sup>			X	X	X	X
Physical Examination <sup>2</sup>		X <sup>2</sup>	X <sup>14</sup>			X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>
12-lead ECG <sup>3</sup>		X <sup>3</sup>	X <sup>3,14</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
ECHO/MUGA	X								
Hematology <sup>4</sup>		X	X <sup>14</sup>			X	X	X	X
Chemistry <sup>5</sup>		X	X <sup>14</sup>		X	X	X	X	X
Coagulation (PT/INR, PTT)		X					X		X
Fasting Serum Glucose <sup>6</sup>		X	X	X	X <sup>6</sup>	X	X	X	X
Glycosylated hemoglobin (HbA1c)		X							X
Fasting Lipid Profile <sup>7</sup>		X							X
Urinalysis <sup>19</sup>		X	X <sup>14</sup>		X	X	X	X	X
Serum or Urine Pregnancy Test <sup>8</sup>		X	X <sup>14</sup>						
PK Timing <sup>9</sup>			X	X	X <sup>9</sup>	X	X		
PBCs Timing <sup>10</sup>			X	X	X	X	X		X

**Table 3-1 Schedule of Events – Escalation Phase, Cycle 1**

Assessments	Screening/Baseline		Treatment						Termination Visit (within 30 days of last dose)
	Within 28 days	Within 14 days	Day 1 (before dose)	Day 1	Day 2	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	
Skin Biopsy for pharmacodynamic assessments <sup>11</sup>		X	X			X	X		
Fresh Tumor Tissue Biopsy <sup>11</sup>		X	X				X		
Collection of Previous Tumor Tissues <sup>12</sup>		X							
MLN0128 Treatment <sup>20</sup>				X	X <sup>20</sup>	X	X	X	
Radiographic Tumor Evaluation and Tumor Markers <sup>13</sup>	X <sup>13</sup>								X <sup>15</sup>
In-Home Daily Fasting Glucose Monitoring <sup>18</sup>					X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	
AE Monitoring <sup>16</sup>				X	X	X	X	X	X
Concomitant Medications <sup>17</sup>	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; CXDY = Cycle X Day Y; CT = computed tomography; DPA = data protection act; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; HbA1c = glycosylated hemoglobin; HIPAA = Health Insurance Portability and Accountability Act; INR = international normalized ratio; PBC = peripheral blood cell; PT = prothrombin time; PTT = partial prothrombin time; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PIC = patient informed consent; PK = pharmacokinetic.

1. Measurement of height will be taken at screening (baseline) only.
2. Complete physical examination at screening, at Cycle 1, Day 1 (C1D1), C1D8, C1D15, and during the Termination visit. A symptom-directed physical examination will be done on C1D22.
3. A 12-Lead ECG will be done at screening/baseline, predose, and at 2 hours (± 30 min) and 4 hours (± 30 min) postdose on C1D1; predose on C1D2 (approximately 24 ± 2 hours after the C1D1 dose, and at 2 hours (± 30 min) postdose on C1D8 and C1D15, and predose on C1D22. A 12-lead ECG will also be obtained at the Termination visit. All scheduled ECGs should be performed after the subject 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. See Section 8.12.1 for details.

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4. Complete blood count (CBC) with white blood cell count (WBC) with differential, hemoglobin (Hgb), hematocrit (Hct), and platelet count. Results of hematology safety labs must be available and reviewed by the investigator prior to MLN0128 dosing.
5. Full chemistry includes Chem 7 (sodium, potassium, chloride, bicarbonate, blood urea nitrogen [BUN], creatinine, glucose), liver function tests (LFTs; ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, albumin, calcium, phosphate, and magnesium. Results of Chem 7 and LFTs safety labs must be available and reviewed by the investigator prior to MLN0128 dosing. Electrolyte levels should be corrected as needed prior to MLN0128 dosing. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.
6. Fasting glucose will be measured predose and at 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min), and 2 hours ( $\pm 30$  min) after dosing on C1D1, predose on C1D2 when the predose PK and PBC samples are drawn (dose escalation phase only), and predose and 2 hours ( $\pm 30$  min) after dosing on C1D8, predose only on C1D15 and C1D22, and at the Termination Visit. Subjects are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) for all of these measurements.
7. Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein (LDL-C), and triglycerides.
8. 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.
9. Plasma PK samples will be obtained for subjects in the dose escalation phase only at predose, 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min), 2 hours ( $\pm 30$  min), 4 hours ( $\pm 30$  min), 8 hours ( $\pm 30$  min), and  $24 \pm 2$  hours postdose on C1D1 (PK draw on Day 2 will be obtained prior to dosing of MLN0128). Additionally, PK will be taken on all subjects in Cycle 1, any day of Days 8-15 when MLN0128 is administered (3 hours  $\pm 1$  hour postdose) when skin biopsy is taken.
10. PBCs will be collected for subjects in the dose escalation phase only at predose, at 2 hours ( $\pm 30$  min), 8 hours ( $\pm 30$  min), and 24 hours ( $\pm 2$  hours) postdose on C1D1, and Cycle 1, any day of Days 8-15 when MLN0128 is administered (3 hours  $\pm 1$  hour postdose) when skin biopsy and PK samples are taken, and at the Termination Visit.
11. Skin biopsies (3 mm core) should be obtained for all subjects within 2 weeks prior to the first dose (can be done on C1D1 prior to dosing) and Cycle 1, any day of Days 8–15 when MLN0128 is administered at 3 hours  $\pm 1$  hour post dose. 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 skin biopsy, PBC, and PK samples at 3 hours  $\pm 1$  hour postdose.
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, pelvis, and relevant tumor markers (eg, CA125, PSA, CA19 9, CA27.29, CA15.3, and CEA) must be obtained within 4 weeks prior to the first dose. The same method (CT with contrast or MRI) must be used throughout the study. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of  $\geq$  PR.
14. The assessment does not need to be repeated if it was done within 3 days prior to the first dose.
15. 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.
16. Adverse events will be collected after administration of the first dose of study drug through 30 days following the last dose of study drug.
17. Concomitant medications will be collected from 30 days prior to the first dose until termination.

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18. Subjects will be given a glucometer on C1D2 to monitor daily fasting glucose levels at home and will be instructed to notify the investigator when the fasting glucose is abnormal (ie,  $\geq 150$  mg/dL). Based on investigator judgment, and based upon the subject achieving a minimum of 6 consecutive months of well-controlled blood glucose levels, the frequency of in-home fasting glucose testing may be reduced to twice weekly. During this period of reduced monitoring, subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL. At any time during the study, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then in-home testing of fasting blood glucose levels will be performed daily with the provided glucometer.
19. 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 if 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 serum creatinine is  $> 1.5 \times$  baseline value.
20. Subjects will be dosed daily until the MTD<sub>qd</sub> is determined. Once the MTD<sub>qd</sub> is determined, subjects will be randomly assigned to a dose cohort for 1 of 3 alternate schedules and dosed either once weekly (QW), once daily for 3 days on, 4 days off each week (QD $\times$ 3d QW), or once daily for 5 days on, 2 days off each week (QD $\times$ 5d QW), in Arms A, B, and C, respectively. Subjects in Arm A (QW), will not be dosed on C1D2. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.

Table 3-2 Schedule of Events – Escalation Phase, Cycle 2 and Beyond

Assessments	Treatment										Termination Visit (within 30 days of last dose)
	Cycle 2						Cycles 3 and 4			Cycle 5 and onward	
	Day 1		Day 2	Day 8	Day 15	Day 22	Day 1	Day 15 (± 2 days)	Day 22 (± 7 days) – Cycle 4 only	Day 1	
	predose	postdose									
Vital signs, weight and ECOG PS	X			X	X	X	X	X		X	X
Physical Exam <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>		X <sup>1</sup>	X <sup>1</sup>				
12-lead ECG <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>		X <sup>2</sup>	X <sup>2</sup>						X
Hematology <sup>3</sup>	X			X	X	X	X	X		X	X
Chemistry <sup>4</sup>	X			X	X	X	X	X		X	X
Coagulation (PT/INR, PTT)	X						X			X	X
Fasting Serum Glucose <sup>5</sup>	X	X			X		X	X		X	X
Glycosylated hemoglobin (HbA1c) <sup>14</sup>							X <sup>15</sup>			X <sup>15</sup>	X
Fasting Lipid Profile <sup>6</sup>	X						X			X	X
Urinalysis <sup>7</sup>	X			X	X	X	X	X		X	X
PK Timing <sup>8</sup>	X	X	X <sup>8</sup>								
PBCs Timing <sup>9</sup>	X	X	X <sup>9</sup>								X
MLN0128 treatment <sup>10</sup>		X		X	X	X	X	X	X	X	
Radiographic tumor evaluation and tumor markers <sup>11</sup>						X			X	X	X <sup>12</sup>
In-home daily fasting glucose monitoring <sup>13</sup>		X <sup>13</sup>		X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>				

**Table 3-2 Schedule of Events – Escalation Phase, Cycle 2 and Beyond**

AE Monitoring <sup>15</sup>	X	X		X	X	X	X	X	X	X	X
Concomitant Medications <sup>16</sup>	X	X		X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; CXDY = Cycle X Day Y; CT = computed tomography; DPA = data protection act; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; HbA1c = glycosylated hemoglobin; HIPAA = Health Insurance Portability and Accountability Act; INR = international normalized ratio; PBC = peripheral blood cell; PT = prothrombin time; PTT = partial prothrombin time; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PIC = patient informed consent; PK = pharmacokinetic.

1. Complete physical examination (PE) will be performed at Day 1 of every cycle and at the Termination visit. Symptom-directed PE will be performed at Days 8, 15, and 22 of Cycle 2 and Day 15 of Cycles 3 and 4.
2. A 12-lead ECG will be obtained at predose and 2 hours ( $\pm 30$  min) postdose at C2D1 and at 2 hours ( $\pm 30$  min) postdose on C2D8 and C2D15. A 12-lead ECG will also be obtained at the Termination visit. All scheduled ECGs should be performed after the subject 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.
3. CBC with WBC with differential, Hgb, Hct, and platelet count. Results of hematology safety labs must be available and reviewed by the investigator prior to MLN0128 dosing.
4. Full chemistry includes Chem 7 (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose), LFTs (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, albumin, calcium, phosphate, and magnesium. Results of Chem 7 and LFTs safety labs must be available and reviewed by the investigator prior to MLN0128 dosing. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.
5. Fasting serum glucose will be done predose on Days 1 and 15 in Cycles 2-4, on Day 1 of every cycle starting from Cycle 5, and at the Termination visit. Subjects are required to fast overnight (nothing except water and/or medications) after midnight or for a minimum of 8 hours for all of these measurements.
6. Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides.
7. Urinalysis will include macroscopic assessment of the amount of protein, glucose, white blood cells, and blood if present (levels should be recorded if available) and microscopic analysis if abnormality is noted. Microscopic urinalysis will be performed along with 12-hr urine collection, spot urine electrolytes, protein and creatinine, and serum chemistry at any time when serum creatinine is  $> 1.5 \times$  baseline value.
8. Plasma PK samples will be obtained for subjects in the dose escalation phase only at predose, 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min), 2 hours ( $\pm 30$  min), 4 hours ( $\pm 30$  min), 8 hours ( $\pm 30$  min) and  $24 \pm 2$  hours postdose on C2D1.
9. PBCs will be collected for subjects in the dose escalation phase only at predose, at 2 ( $\pm 30$  min), 8 hours ( $\pm 30$  min) and  $24 + 2$  hours postdose on C2D1, and during the Termination visit.
10. Subjects will be dosed daily until the MTD<sup>qd</sup> is determined. Once the MTD<sup>qd</sup> is determined, subjects will be randomly assigned to 1 of 3 alternate dosing schedules and dosed either once weekly (QW), once daily for 3 days on, 4 days off each week (QD $\times$ 3d QW), or once daily for 5 days on, 2 days of each week (QD $\times$ 5d QW), in Arms A, B, or C, respectively. Subjects in Arm A (QW) will not be dosed on C2D2. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.

**Table 3-2 Schedule of Events – Escalation Phase, Cycle 2 and Beyond**

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11. CT (with contrast)/MRI of chest, abdomen, pelvis, and relevant tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA) will be obtained every 2 cycles ( $\pm$  7 days). For long-term patients, defined as study participation  $\geq$  3 years, a CT (with contrast)/MRI of chest, abdomen, pelvis, and relevant tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA) will be obtained at intervals of up to every 4 cycles ( $\pm$  7 days), as clinically indicated. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of  $\geq$  PR. The same method (CT with contrast or MRI) must be used throughout the study.
  12. 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.
  13. Subjects will be given a glucometer on CID1 to monitor daily fasting glucose levels at home and will be instructed to notify the investigator when the fasting glucose is abnormal (ie,  $\geq$  150 mg/dL). Based on investigator judgment, and based upon the subject achieving a minimum of 6 consecutive months of well-controlled blood glucose levels, the frequency of in-home fasting glucose testing may be reduced to twice weekly. During this period of reduced monitoring, subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL. At any time during the study, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then in-home testing of fasting blood glucose levels will be performed daily with the provided glucometer.
  14. Beginning with Cycle 4, HbA1c sampling should occur on Day 1 and every 3 months thereafter.
  15. Adverse events will be collected after administration of the first dose of study drug through 30 days after the last dose of study drug.
  16. Concomitant medications will be collected from 30 days before the first dose of study drug until the termination.

## Schedule of Events for the Expansion Phase

Table 3-3 Schedule of Events – Expansion Phase, Cycle 1

Assessments	Screening/Baseline		Treatment					Termination Visit (within 30 days of last dose)
	Within 28 days	Within 14 days	Day 1 (before dose)	Day 1	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	
Informed Consent/PIC and HIPAA/DPA	X							
Medical history	X							
Vital signs, height <sup>1</sup> , weight, and ECOG PS		X <sup>1</sup>	X <sup>12</sup>		X	X	X	X
Physical examination <sup>2</sup>		X <sup>2</sup>	X <sup>2,12</sup>		X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>
12-lead ECG <sup>3</sup>		X	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X
ECHO/MUGA	X							
Hematology <sup>4</sup>		X	X <sup>12</sup>		X	X	X	X
Chemistry <sup>5</sup>		X	X <sup>12</sup>	X	X	X	X	X
Coagulation (PT/INR, PTT)		X				X		X
Fasting Serum Glucose <sup>6</sup>		X	X	X	X	X	X	X
Glycosylated hemoglobin (HbA1c)		X						X
Fasting Lipid Profile <sup>7</sup>		X						X
Urinalysis <sup>17</sup>		X	X <sup>12</sup>	X	X	X	X	X
Serum or Urine Pregnancy Test <sup>8</sup>		X	X <sup>12</sup>					
PK Timing <sup>9</sup>	See Table 3-5, Expansion Phase Sparse PK Sampling Scheme							
Collection of Previous Tumor Tissues <sup>10</sup>		X						
MLN0128 Treatment <sup>18</sup>				X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	
Circulating tumor DNA <sup>19</sup>	X							X
Radiographic Tumor Evaluation	X <sup>11</sup>							X <sup>13</sup>

**Table 3-3 Schedule of Events – Expansion Phase, Cycle 1**

and Tumor Markers <sup>11</sup>								
In-Home Daily Fasting Glucose Monitoring <sup>16</sup>				X <sup>16</sup>	X <sup>16</sup>	X <sup>16</sup>	X <sup>16</sup>	
AE Monitoring <sup>14</sup>				X	X	X	X	X
Concomitant Medications <sup>15</sup>	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; CXDY = Cycle X Day Y; CT = computed tomography; DPA = data protection act; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; HbA1c = glycosylated hemoglobin; HIPAA = Health Insurance Portability and Accountability Act; INR = international normalized ratio; PT = prothrombin time; PTT = partial prothrombin time; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PIC = patient informed consent; PK = pharmacokinetic.

- The height measurement will be taken at screening (baseline) only.
- Complete physical examination at screening, at Cycle 1, Day 1 (C1D1), C1D8, C1D15, and during the Termination visit. Symptom-directed physical examination will be done on C1D22.
- A 12-Lead ECG will be done at screening/baseline, predose and at 2 hours ( $\pm 30$  min) and 4 hours ( $\pm 30$  min) postdose on C1D1; and at 2 hours ( $\pm 30$  min) postdose on C1D8 and C1D15, and predose on C1D22. A 12-lead ECG will also be obtained at the Termination visit. All scheduled ECGs should be performed after the subject 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.
- Complete blood count (CBC) with white blood cell count (WBC) with differential, hemoglobin (Hgb), hematocrit (Hct), and platelet count. Results of hematology safety labs must be available and reviewed by the investigator prior to MLN0128 dosing.
- Full chemistry includes Chem 7 (sodium, potassium, chloride, bicarbonate, blood urea nitrogen [BUN], creatinine, glucose), liver function tests (LFTs; ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, albumin, calcium, phosphate, and magnesium. Results of Chem 7 and LFTs safety labs must be available and reviewed by the investigator prior to MLN0128 dosing. Electrolyte levels should be corrected as needed prior to MLN0128 dosing. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.
- Fasting glucose will be measured predose and at 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min) and 2 hours ( $\pm 30$  min) after dosing on C1D1; and predose and 2 hours ( $\pm 30$  min) after dosing on C1D8; predose only on C1D15 and C1D22; and at the Termination Visit. Subjects are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) for all of these measurements.
- Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein (LDL-C), and triglycerides.
- 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.
- See Table 3-5 for specific PK sampling times during the expansion phase.
- 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

**Table 3-3 Schedule of Events – Expansion Phase, Cycle 1**

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- drug treatment, if extra time is needed to locate the specimens.
11. Baseline CT (with contrast)/MRI of chest, abdomen, pelvis, and relevant tumor markers (eg, CA125, PSA, CA19 9, CA27.29, CA15.3, and CEA) must be obtained within 4 weeks prior to the first dose. The same method (CT with contrast or MRI) must be used throughout the study. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of  $\geq$  PR.
  12. The assessment does not need to be repeated if it was done within 3 days prior to the first dose.
  13. 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.
  14. Adverse events will be collected after administration of the first dose of study drug through 30 days following the last dose of study drug.
  15. Concomitant medications will be collected from 30 days prior to the first dose until the Termination visit.
  16. Subjects will be given a glucometer on C1D1 to monitor daily fasting glucose levels at home and will be instructed to notify the investigator when the fasting glucose is abnormal (ie,  $\geq$  150 mg/dL). Based on investigator judgment and based upon the subject achieving a minimum of 6 consecutive months of well-controlled blood glucose levels, the frequency of in-home fasting glucose testing may be reduced to twice weekly. During this period of reduced monitoring, subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL. At any time during the study, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then in-home testing of fasting blood glucose levels will be performed daily with the provided glucometer.
  17. 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 if 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 serum creatinine is  $>$  1.5 baseline value.
  18. Timing of MLN0128 administration will depend on dosing schedule(s) selected for the expansion phase. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.
  19. Circulating tumor DNA also at C5D1 and end of treatment.

**Table 3-4 Schedule of Events – Expansion Phase, Cycle 2 and Beyond**

Assessments	Treatment									Termination Visit (within 30 days of last dose)
	Cycle 2					Cycles 3 and 4			Cycle 5 and onward	
	Day 1		Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1	Day 15 (± 2 days)	Day 22 (± 7 days) – Cycle 4 only	Day 1	
	Predose	postdose								
Vital signs, weight, and ECOG PS	X		X	X	X	X	X		X	X
Physical Exam <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>	X <sup>1</sup>
12-lead ECG <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>						X <sup>2</sup>
Hematology <sup>3</sup>	X		X	X	X	X	X		X	X
Chemistry <sup>4</sup>	X		X	X	X	X	X		X	X
Coagulation (PT/INR, PTT)	X					X			X	X
Fasting Serum Glucose <sup>5</sup>	X			X		X	X		X	X
Glycosylated hemoglobin (HbA1c) <sup>13</sup>						X <sup>13</sup>			X <sup>13</sup>	X
Fasting Lipid Profile <sup>6</sup>	X					X			X	X
Urinalysis <sup>7</sup>	X		X	X	X	X	X		X	X
PK Timing <sup>8</sup>	See Table 3-5, Expansion Phase Sparse PK Sampling Scheme									
MLN0128 treatment <sup>9</sup>		X	X	X	X	X	X	X	X	
Radiographic tumor evaluation and tumor markers <sup>10</sup>					X			X	X	X <sup>11</sup>
In-home daily fasting glucose monitoring <sup>12</sup>		X	X	X	X	X	X	X	X	
AE Monitoring <sup>14</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Medications <sup>15</sup>	X	X	X	X	X	X	X	X	X	X
Circulating tumor DNA <sup>16</sup>									X	X

Abbreviations: AE = adverse event; CXDY = Cycle X Day Y; CT = computed tomography; DPA = data protection act; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; HbA1c = glycosylated hemoglobin; HIPAA = Health Insurance Portability and Accountability Act; INR = international normalized ratio; PT = prothrombin time; PTT = partial prothrombin time; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PIC = patient informed consent; PK = pharmacokinetic.

1. Complete physical examination (PE) will be performed at Day 1 of every cycle and at the Termination visit. Symptom-directed PE will be performed at Days 8, 15, and 22 of Cycle 2 and Day 15 of Cycles 3 and 4.
2. A 12-lead ECG will be obtained at predose and 2 hours ( $\pm 30$  min) postdose at C2D1 and at 2 hours ( $\pm 30$  min) postdose on C2D8 and C2D15. A 12-lead ECG will also be obtained at the Termination visit. All scheduled ECGs should be performed after the subject 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.
3. CBC with WBC with differential, Hgb, Hct, and platelet count. Results of hematology safety labs must be available and reviewed by the investigator prior to MLN0128 dosing.
4. Full chemistry includes Chem 7 (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose), LFTs (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, albumin, calcium, phosphate, and magnesium. Results of Chem 7 and LFTs safety labs must be available and reviewed by the investigator prior to MLN0128 dosing. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.
5. Fasting serum glucose will be done predose on Days 1 and 15 in Cycles 2 to 4, on Day 1 of every cycle starting from Cycle 5, and at the Termination visit. Subjects are required to fast overnight (nothing except water and/or medications) after midnight or for a minimum of 8 hours for all of these measurements.
6. Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein (LDL-C), and triglycerides.
7. Urinalysis will include macroscopic assessment of the amount of protein, glucose, white blood cells, and blood if present (levels should be recorded if available) and microscopic analysis if abnormality is noted. Microscopic urinalysis will be performed along with 12-hr urine collection, spot urine electrolytes, protein and creatinine, and serum chemistry at any time when serum creatinine is  $> 1.5$  baseline value.
8. See [Table 3-5](#) for specific PK sampling times during the expansion phase.
9. Timing of MLN0128 administration will depend on dosing schedule(s) selected for the expansion phase. Electrolyte levels should be corrected as needed prior to MLN0128 dosing.
10. CT (with contrast)/MRI of chest, abdomen, pelvis, and relevant tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA) will be obtained every 2 cycles ( $\pm 7$  days). For long-term patients, defined as study participation  $\geq 3$  years, a CT (with contrast)/MRI of chest, abdomen, pelvis, and relevant tumor markers (eg, CA125, PSA, CA19-9, CA27.29, CA15.3, and CEA) will be obtained at intervals of up to every 4 cycles ( $\pm 7$  days), as clinically indicated. A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of  $\geq$  PR. The same method (CT with contrast or MRI) must be used throughout the study.
11. 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.
12. Subjects will be given a glucometer on C1D1 to monitor daily fasting glucose levels at home and will be instructed to notify the investigator when the fasting glucose is abnormal (ie,  $\geq 150$  mg/dL). Based on investigator judgment, and based upon the subject achieving a minimum of 6 consecutive months of well-controlled blood glucose levels, the frequency of in-home fasting glucose testing may be reduced to twice weekly. During this period of

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reduced monitoring, subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL. At any time during the study, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then in-home testing of fasting blood glucose levels will be performed daily with the provided glucometer.

13. Beginning with Cycle 4, HbA1c sampling should occur on Day 1 and every 3 months thereafter.

14. Adverse events will be collected after administration of the first dose of study drug through 30 days following the last dose of study drug.

15. Concomitant medications will be collected from 30 days before first dose until the Termination visit.

16. Circulating tumor DNA at C5D1 and end of treatment.

## Pharmacokinetic Sampling Scheme in the Expansion Phase

Table 3-5 Expansion Phase Sparse Pharmacokinetic Sampling Scheme for Population Pharmacokinetic Analysis

Expansion Treatment Schedules	Study Cycle	Study Day	Sampling Time (window)	Plasma PK Sample
	1	1	Pre-dose (within 30 min of dosing)	X
	1	1	2 h ± 30 min	X
• QD	1	1	4 h ± 30 min	X
• QDx3d QW	1	1	6 h ± 30 min	X
• QDx5d QW	1	8, 15, or 22	Pre-dose (within 30 min of dosing)	X
• QW			2 h ± 1 h	X
	4 <sup>a</sup>	16 <sup>a</sup>	Any time during clinic visit	X <sup>a</sup>
Total number of planned PK samples				6 (or 7 <sup>a</sup> )

Abbreviations: min = minutes; PK = pharmacokinetics; QD = once daily; QDx3d QW = once daily for 3 days on, 4 days off, repeated each week; QDx5d QW = once daily for 5 days on, 2 days off, repeated each week; QW = once weekly

a For the QW schedule only, a PK sample will be obtained based on observed tolerance and investigator discretion, on Cycle 4, Day 16, approximately 24 hours after administration of the Cycle 4, Day 15 weekly dose of MLN0128 at home. The Cycle 4 clinic visit will be delayed 1 day from Day 15 to Day 16 to allow for collection of this PK sample and to complete the planned Cycle 4, Day 15 safety assessments. Subjects will be instructed to note the time of at-home MLN0128 dosing and this time will be recorded in the PK sampling log.

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**5. LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS**

AE	Adverse Event
AKT	Serine/Threonine Protein Kinase (also PKB; Serine/Threonine Protein Kinase B)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration-time curve
AUC <sub>0-24</sub>	Area under the plasma concentration-time curve from 0 to 24 hr
AUC <sub>0-last</sub>	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
AUC <sub>0-∞</sub>	Area under the plasma concentration-time curve from time zero to infinity
BRAF	V-raf murine Sarcoma Viral Oncogene Homolog B1
BUN	Blood Urea Nitrogen
C <sub>max</sub>	Maximum Plasma Concentration
C <sub>max,ss</sub>	Maximum steady-state plasma concentration
C <sub>min</sub>	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
Cleaved Caspase 3	Cleaved Cysteine-aspartic Acid Protease 3
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
DLT	Dose Limiting Toxicity
DPA	Data Protection Act
4EBP1	Eukaryotic Initiation Factor 4E-binding Protein 1
EC	Ethics Committee

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ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
ERBB2	Epidermal Growth Factor Receptor 2
ERK	Extracellular Signal-regulated Kinase
FBG	Fasting Blood Glucose
FDA	Food and Drug Administration
FBXW7	F-box and WD repeat domain containing 7
FOXO	Forkhead Box O
FSG	Fasting Serum Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GOLPH3	Golgi Phosphoprotein 3
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.
MLN0128	Also known as TAK-228
MRI	Magnetic Resonance Imaging

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MTD	Maximum Tolerated Dose
mTOR	Mechanistic (formerly Mammalian) Target of Rapamycin
MUGA	Multiple Gated Acquisition Scan
Myc (N/C)	C-Myc, N-Myc oncogene
NCI	National Cancer Institute
NDRG1	N-Myc Downstream Regulated 1
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
QDx3 QW	Once a day 3 on 4 days off repeated each week
QDx5 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

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S6K	Ribosomal S6 kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
STD <sub>10</sub>	Severely Toxic Dose to 10% of rats
t <sub>1/2</sub>	Plasma Half-life
T <sub>max</sub>	Time of maximum plasma concentration
TORC	Target of Rapamycin Complex
TORC1	Target of Rapamycin Complex 1
TORC2	Target of Rapamycin Complex 2
TORC1/2	Target of Rapamycin Complex 1 and 2
TSC1/2	Tuberous sclerosis complex 1/2
ULN	Upper Limit of Normal
UPSC	Uterine Papillary Serous Carcinoma
US	United States
VHL	Von Hippel-Lindau Tumor Suppressor
WBC	White blood cell

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## **6. INTRODUCTION**

MLN0128 (also known as TAK-228 and INK128) is a potent and highly selective, adenosine triphosphate (ATP)-competitive inhibitor of the serine/threonine kinase termed the mechanistic (formerly, 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 (TORC1) and mTOR complex 2 (TORC2). 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.

### **6.1 Nonclinical Studies**

Nonclinical studies have been conducted to demonstrate the mechanism of action, efficacy, and safety of MLN0128 in biological models to characterize pharmacodynamics, define the pharmacokinetic (PK) properties, characterize the toxicity profile, and support a safe starting dose in humans for MLN0128 drug product.

The pharmacology studies conducted with MLN0128 identified it as an orally active, potent, and selective inhibitor of the serine/threonine protein kinase mTOR in both cellular signaling complexes, TORC1 and TORC2. In a biochemical assay, MLN0128 inhibited mTOR with a concentration inhibiting enzyme activity by 50% (IC<sub>50</sub>) of 1.1 nM. When tested against the closely structural-related phosphoinositol-3-kinases (PI3Ks), the MLN0128 IC<sub>50</sub> values were increased more than 100-fold over mTOR potency, establishing a large selectivity window. In cellular models, MLN0128 displayed inhibition of TORC1/2 signaling pathways with IC<sub>50</sub>s less than 10 nM. In human tumor mouse xenograft models of a wide range of tissue types and varying genetic backgrounds, such as glioblastoma (U87), non-small cell lung cancer (A549), breast cancer (ZR-75-1), renal cell cancer (786-O), and endometrial cancer (AN3-CA), MLN0128 inhibited pharmacodynamic (PD) markers of TORC1/2 pathways that correlate with strong tumor growth inhibition in a specific and dose-dependent manner. Treatment with MLN0128 significantly ameliorated tumor growth in mice at well-tolerated doses.

Secondary pharmacology studies using commercial, in vitro receptor binding assays revealed MLN0128 had affinity for binding 2 adenosine receptors at concentrations

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(~10  $\mu\text{M}$ ) well above expected therapeutic drug concentrations. Similarly, MLN0128 displayed low potential ( $\text{IC}_{50} = 175 \mu\text{M}$ ) to affect the human ether-a-go-go related (hERG) potassium channel, and displayed no effect on electrocardiograms obtained from conscious telemeterized monkeys. Based on this profile, the anticipated risk for clinically deleterious cardiovascular effects is considered low.

MLN0128 displayed consistent and predictable pharmacokinetic parameters across mouse, rat, dog, and cynomolgus monkey. It was rapidly absorbed after oral delivery (time of first maximum plasma concentration [ $T_{\text{max}}$ ] ranged from 0.25 hr-6.0 hr), showed high oral bioavailability (30%-91%) and dose-proportional plasma exposures. Plasma to brain concentration ratios of 5- to 10-fold in the mouse indicated a moderate propensity for MLN0128 to cross the blood-brain barrier. MLN0128 was modestly bound (70.5%) to human plasma proteins. Allometric scaling of the animal data to human predicts a low clearance ( $\text{CL} \sim 2.1 \text{ mL/min/kg}$ ), a small volume of distribution ( $V_{\text{ss}} \sim 1.2 \text{ L/kg}$ ), and a plasma half-life ( $t_{1/2}$ ) amenable to once-daily administration ( $t_{1/2} \sim 15\text{-}30 \text{ hr}$ ).

Multiple phase I/II metabolic pathways, including hydroxylation and glucuronidation, have been identified for MLN0128. The metabolites generated in human microsomal incubations were also observed in rats and monkeys, the species studied in Good Laboratory Practice (GLP) toxicology studies. The dog (either in vitro or in vivo) did not produce any phase I metabolites formed in human microsomal incubations.

The human cytochrome P450 (CYP) isoforms CYP3A4, CYP2C9, and CYP2C19 contribute to MLN0128 metabolism. MLN0128 displayed low potential ( $\text{IC}_{50} \geq 30 \mu\text{M}$ ) as a direct inhibitor of the major human CYP isoforms (CYP1A2, CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6). Recently completed in vitro metabolism experiments in human hepatocytes using  $^{14}\text{C}$ -labeled MLN0128 suggest that MLN0128 is metabolized primarily via CYP1A2 (approximately 31%-40%), with a minor contribution from CYP3A4 (approximately 11%-22%). These data suggest that MLN0128 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-CYP, non-uridine diphosphate glucuronosyltransferase pathway (approximately 18%). The new data differ from the previous in vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in MLN0128 metabolism. MLN0128 does not inhibit or induce any of the major CYP enzymes. In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with

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MLN0128 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers (see Section 21.2) should only be administered with caution and at the discretion of the investigator during the study.

The MLN0128 toxicology program consisted of oral single-dose studies in rats, dogs, and monkeys, repeat-dose studies in rats (non-GLP 4-day, non-GLP 14-day, and GLP 28-day with 14 days recovery) and monkeys (non-GLP 14-day and GLP 28-day with 14 days recovery), a GLP cardiac safety pharmacology study in telemeterized monkeys, and a GLP Ames assay. MLN0128 freebase drug substance (Form A) was used in all these studies and will be used in phase 1 clinical studies.

In dogs and monkeys, clinical signs were observed following single intravenous and oral doses of MLN0128. Dogs received an intravenous (IV) dose of 1 mg/kg (20 mg/m<sup>2</sup>) or an oral (PO) dose of 3 mg/kg (60 mg/m<sup>2</sup>); all animals were euthanized in extremis at 3-days postdose with signs of gastrointestinal distress, decreased activity, decreased body temperature, and decreased food intake. Post-mortem gross examinations defined all tissues within normal limits. In the monkey, IV and PO doses were administered at 1 mg/kg (12 mg/m<sup>2</sup>) and 3 mg/kg (36 mg/m<sup>2</sup>), respectively; all animals displayed clinical signs of emesis, decreased activity, and decreased food intake. Clinical signs persisted up to 7-days postdose. Supportive care consisting of heat lamps, subcutaneous fluids, and supplemental food offerings (fruits and vegetables) appeared to aid in the resolution of clinical signs. Animals recovered by 10 days postdose. The overdoses and associated plasma exposures exceeded those at the subsequently defined Highest Non-Severely Toxic Dose (HNSTD) of 0.15 mg/kg/day (1.8 mg/m<sup>2</sup>/day) in monkeys by 7 to 33-fold.

The toxicity profiles in rats from the 14-day and 28-day studies were consistent. In the 28 day repeat-dose with 14-day recovery rat study, dose-related increases in toxicity were observed; no effects at 0.3 mg/kg/day (1.8 mg/m<sup>2</sup>/day), no significant adverse effects at 1.0 mg/kg/day (6.0 mg/m<sup>2</sup>/day), and mild to moderate effects at 3 mg/kg/day (18 mg/m<sup>2</sup>/day).

The effects seen at the 3.0-mg/kg/day dose were 26% body weight decreases as compared to controls. Clinically significant changes observed in clinical chemistry parameters with increases in aspartate aminotransferase, glucose, and insulin; decreases in leukocytes, lymphocytes, and eosinophils; and histopathological changes in the bone marrow (hypocellularity), thymus (lymphoid necrosis), testes (degeneration/atrophy), epididymides (oligospermia), ovaries (abnormal estrous cycle), and lungs (alveolar histiocytosis). A

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functional observational battery (FOB) test (conducted on study Days 1, 2, and 27) observed a mild change in gait only in the high-dose males on Day 27. The MLN0128 plasma exposures (maximum plasma concentration [ $C_{max}$ ] and area under the concentration-time curve from time 0 to time of last measurable concentration [ $AUC_{0-last}$ ]) increased dose-proportionally between 0.3 to 3.0 mg/kg/day with no difference between male and female rats and the toxicokinetic parameters were similar between Day 1 and Day 28.

Following a 14-day recovery period, all test-article related findings were resolved to normal levels, demonstrating reversibility of MLN0128 induced toxicities in the rat. Based on the data from the 28-day, repeat-dose, rat study, the dose of 3 mg/kg/day (18 mg/m<sup>2</sup>/day) was considered the rodent STD<sub>10</sub> (severely toxic dose to 10% of rats).

In the 28-day, repeat-dose, GLP, cynomolgus monkey study, MLN0128 toxicities were dose related and were either absent or tended toward normal at the end of the 14-day recovery period. The high dose (0.3 mg/kg/day [3.6 mg/m<sup>2</sup>/day]) resulted in severe toxicities that led to the moribund sacrifice of 2 monkeys, discontinuation of dosing, and the end of study assessments on Day 19. MLN0128-related effects observed at the high dose included clinical signs of 10% body weight decreases as compared to baseline, decreased appetite, abnormal posture, decreased activity, and decreased body temperature. Clinical chemistry changes were increases in aspartate aminotransferase, creatinine kinase (MM isoform), cholesterol, triglycerides, and insulin; and decreases in sodium, potassium, and phosphorus. Hematology parameter alterations were decreases in lymphocytes and increases in neutrophils and monocytes. Milder effects were observed at 0.15 mg/kg/day (1.8 mg/m<sup>2</sup>/day). The low dose (0.05 mg/kg/day [0.6 mg/m<sup>2</sup>/day]) produced only some instances of test-article related organ weight changes; weight decreases in thymus (statistically significant) and in spleen, and weight increases in adrenals.

Histopathological changes at the 0.15-mg/kg/day and 0.3-mg/kg/day doses were seen in the thymus, spleen, lymph nodes, gut-associated lymphoid tissue, bone marrow, adrenal glands, salivary glands, gastrointestinal tract, skin, and epididymides. In the recovery animals, findings were limited to the thymus (minimal to mild lymphoid depletion). Specific MLN0128-related microscopic findings in the lymphoid organs, including gut-associated lymphoid tissue, were multicentric lymphoid depletion and splenic red pulp depletion. At the high dose, the spleen had moderate to severe depletion of red blood cells and hematopoietic cells. In bone marrow, minimal to moderate mixed cell depletion was seen. In adrenals, minimal to moderate bilateral cortical hypertrophy/hyperplasia was evident. In the pancreas, there was minimal to severe acinar cell secretory depletion. Similar findings

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were seen in the parotid and mandibular salivary glands at the high dose. In the gastrointestinal tract, there were findings in the cardiac and pyloric stomach of minimal to mild erosion/ulceration, edema, hemorrhage, and acute inflammation; in the ileum of 1 high-dose male, minimal hemorrhage; and in 1 high-dose female, mild mucosal atrophy. In the jejunum, colon, and rectum, there were findings of minimal dilatation of mucosal glands; and in the rectum, minimal to mild erosion/ulceration. At the high dose (0.3 mg/kg/day), some monkeys exhibited mild to moderate erosion/ulceration and minimal to moderate epidermal hyperplasia of the skin on the face, neck, and forelimbs; the effect was considered possibly related to test article, debilitation, or self-trauma. In the epididymides of all controls and treated males there were severe bilateral oligospermia considered indicative of sexual immaturity.

In the recovery monkeys, test article-related findings of minimal to mild lymphoid depletion were limited to thymus in females at 0.15 mg/kg/day and in both sexes at 0.30 mg/kg/day. This lymphoid depletion was of lesser severity than that noted at the terminal necropsy indicating partial resolution over the recovery period.

Electrocardiography conducted on all animals at baseline, Day 1, and Day 27 demonstrated no test article effects. This was consistent with the lack of significant findings in the GLP-compliant, cardiovascular, safety pharmacology study conducted in conscious monkeys.

MLN0128 plasma exposures ( $C_{\max}$  and  $AUC_{0-\text{last}}$ ) increased in a dose-proportional manner between 0.05 to 0.30 mg/kg/day with no difference observed between male and female monkeys. Steady-state plasma exposures (Day 19 or Day 28  $AUC_{0-\text{last}}$  for high or mid/low doses, respectively) were 0.8-fold to 2.7-fold higher than those obtained on Day 1 consistent with  $t_{1/2S}$  of 5 to 16 hours that suggest this level of accumulation.

On the basis of the data from the 28-day, GLP, repeat-dose, monkey study, a dose of 0.05 mg/kg/day was well tolerated, minimal to moderate toxicities were observed at 0.15 mg/kg/day, and a dose of 0.3 mg/kg/day produced dose-limiting, severe toxicity. Thus, the HNSTD in monkeys was considered to be 0.15 mg/kg/day (1.8 mg/m<sup>2</sup>/day).

## **6.2 Clinical Experience With MLN0128**

A detailed review of the safety and PK profile observed with MLN0128 can be found in the MLN0128 Investigator's Brochure (IB).

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#### 6.2.1 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  $\geq 3$  have been reported in  $\leq 10\%$  of subjects and include hyperglycemia, asthenia, mucosal inflammation, anemia, lymphopenia, hypophosphatemia, and rash. Inclusive of all grades, the most frequently reported AEs (those with  $\geq 20\%$  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 the 13 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  $\geq 3$  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  $\geq 20\%$  incidence) include

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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<sup>2</sup>) 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.

#### **6.2.2 Clinical Pharmacokinetics**

MLN0128 displays high oral bioavailability and predictable PK with minimal levels of steady state accumulation. It is rapidly absorbed with T<sub>max</sub> 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<sub>max,ss</sub>) ranged from 52 to 232 nM. Comparisons of plasma exposures (C<sub>max</sub> and area under the plasma concentration-time curve from 0 to 24 hr [AUC<sub>0-24</sub>]) following oral doses of MLN0128 suggest dose-linear plasma pharmacokinetics.

#### **6.3 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.<sup>(2)</sup> The mTOR activity in the

intracellular signaling complexes (TORC1 and TORC2) 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, TORC1 and TORC2. TORC1, 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 4 binding proteins (4EBPs).<sup>(3)</sup> Rapamycin (Rapamune<sup>®</sup>) is a TORC1 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 the development of new 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 (Torisel<sup>®</sup>) was approved by the United States (US) Food and Drug Administration (FDA) for treatment of advanced renal cell cancer and, in March 2009, everolimus (Afinitor<sup>®</sup>) was approved for treatment of advanced renal cancer after failure of treatment with sunitinib or sorafenib.<sup>(4,5)</sup> 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 TORC1 (without inhibition of TORC2) leads to activation of serine/threonine protein kinase B (AKT) due to a feedback mechanism, and this upregulation of AKT may actually accelerate tumor progression, thus limiting the clinical efficacy of rapalogs.<sup>(6)</sup>

Additionally, TORC2 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 TORC2 inhibition has been explored for anticancer therapeutics and preclinical investigations have shown inhibition of TORC2 blocks cancer growth.<sup>(7)</sup> TORC2 inhibition can also reverse the activation of AKT induced by TORC1 inhibition. Therefore, mTOR inhibitors that target

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both mTOR complexes such as MLN0128 may achieve greater clinical efficacy than rapalogs.<sup>(8)</sup>

To date, INK128-001 has evaluated in QD, QW, QD×3d QW, and QD×5d QW dosing schedules in subjects with advanced malignancies.

The PI3K/mTOR pathway is central to a number of vital cellular functions, such as cell growth, translational control, angiogenesis, and survival. Dysregulation of this pathway has been implicated in many types of human cancers.<sup>(2)</sup> In the expansion phase, patients with the following tumor types will be enrolled based on the recognized importance of the PI3K/mTOR pathway in each: renal, endometrial, and bladder. The significance of the PI3K/mTOR pathway in each of these tumor types is presented in the following.

*Renal Cancer:* mTOR controls cell growth, proliferation, and survival and plays a critical role in the pathogenesis of renal cell carcinoma (RCC).<sup>(9)</sup> mTOR frequently shows alterations in the mTOR signaling pathway, either increasing mTOR activity or, depending on mTOR activation for their oncogenic potential, mTOR controls production of HIF-1 $\alpha$ , an important protein in RCC, where its unregulated activity is causally related to disease pathogenesis.<sup>(10)</sup> The HIF transcription factors drive the expression of hypoxic stress response genes, which include angiogenic growth factors, such as VEGF, PDGF- $\beta$ , TGF- $\alpha$ , and Ang-1. PTEN is frequently lost in RCC, which stimulates mTOR activity through enhancement of the PI3K/AKT pathway. Loss of PTEN is correlated with survival and indicates a poorer prognosis.<sup>(11)</sup> Two partial TORC1 inhibitors, temsirolimus and everolimus, have already been approved for the treatment of RCC. MLN0128 is a potent inhibitor of TORC1 and TORC2. It shows strong inhibition of RCC cells regardless of their genetic backgrounds. MLN0128 also displays potent anti-tumor efficacy in various preclinical RCC tumor models.<sup>(12)</sup>

*Endometrial Cancer:* The PI3K pathway is frequently hyper-activated in endometrial cancer through various PI3K/AKT activating mutations (such as phosphatase and tensin homolog [PTEN] and phosphoinositide-3-kinase alpha catalytic subunit [PIK3CA]).<sup>(13)</sup> The finding of PTEN mutations in 40% to 60% of endometrial cancers and PIK3CA mutations in 23%, suggests this pathway is important in the pathogenesis of this disease.<sup>(14)</sup> Loss of PTEN leads to constitutive activation of AKT, which in turn leads to up-regulation of mTOR. The PIK3CA mutations are nonsynonymous missense mutations that confer constitutive kinase activity rendering the PI3K/mTOR pathway hyperactivated. MLN0128 potently inhibits proliferation of endometrial cells with PTEN and PI3K $\alpha$  mutations in vitro. It displays

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single agent anti-tumor activity in preclinical tumor models and enhances the efficacy of standard-of-care chemotherapeutic agents such as paclitaxel and docetaxel.<sup>(15, 16)</sup>

*Bladder Cancer:* PI3K/mTOR pathway activation is involved in bladder cancer tumorigenesis and development. This pathway can be activated by multiple components. PI3K- $\alpha$  mutation is detected in about 25% of bladder cancers.<sup>(17)</sup> Over 10% of bladder cancers show mutations in PTEN and TSC1 genes.<sup>(17)</sup> The expression of pAkt, p4EBP1, and pS6 is significantly higher in high-grade and advanced-stage bladder cancers and is associated with poorer prognosis.<sup>(18, 19)</sup> Rapalogs have been shown to inhibit bladder cancer cell proliferation and induce apoptosis in vitro, and inhibit bladder tumor growth in mouse models.<sup>(20, 21)</sup> MLN0128, which more potently inhibits pAKT and p4EBP1 than rapalogs, could be exploited as a potential therapeutic strategy in bladder cancer.

#### 6.4 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 (hypercholesterolemia 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 (about 20%); arthralgia (25%-30%); asthenia (about 30%); peripheral edema (24%-35%).<sup>(22, 23, 24, 25)</sup> Serious infections have included sepsis, opportunistic infections, and even death. An increase in the

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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.<sup>(23, 24, 25)</sup>

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.

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### 7. STUDY OBJECTIVES

The primary objectives of the study are:

- To determine the MTD and DLT of oral administration of MLN0128 given daily or via alternate dosing schedules in subjects with advanced malignancies
- To evaluate the safety and tolerability of orally administered single-agent MLN0128, given daily or via alternate dosing schedules, in both the dose escalation and the expansion phases of the study

The secondary objectives of the study are:

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

The exploratory objectives of the study are:

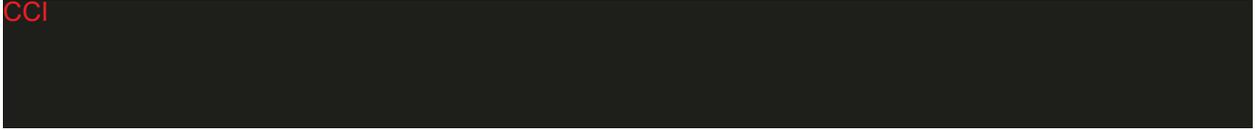
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## **8. INVESTIGATIONAL PLAN**

### **8.1 Overall Study Design and Plan**

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

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

### **8.2 Dose Escalation Phase**

Up to 4 different dosing schedules will be explored in the dose escalation phase: QD, QW, QDx3d QW, and QDx5d QW. The MTD for the QD schedule of MLN0128 in subjects with advanced solid malignancies was determined to be 6 mg ( $MTD^{qd} = 6 \text{ mg}$ ) on the basis of the initial evaluation of 6 subjects in this cohort.

After the MTD was determined for the once-daily dosing schedule ( $MTD^{qd} = 6 \text{ mg}$ ), study of the additional dosing schedules began with implementation of Amendment 7. Enrollment was initiated in 2 parallel and independent arms: Arm A with once-weekly dosing starting at a dose not to exceed that of twice the  $MTD^{qd}$ ; and Arm B with MLN0128 administered QDx3d QW starting at the  $MTD^{qd}$ . Amendment 10 added a further dosing schedule as noted, QDx5d QW. Subjects are randomly assigned to an alternate dosing arm when all arms are open for enrollment at the same time. Subjects may not participate in more than 1 dosing arm.

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In the absence of unacceptable MLN0128 treatment-related toxicity or disease progression, subjects may receive MLN0128 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.

#### 8.2.1 Dose-Limiting Toxicity

Dose-limiting toxicities (DLTs) are defined according to the adverse event profile observed during the first 28 days of drug administration in the dose escalation phase of the study and as described in [Table 8-1](#). Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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>. All AEs should be considered possibly related to the study drug unless such relationship can be definitively excluded.

Dose-limiting toxicity is defined as any of the following MLN0128-related toxicities that occur within the first 28 days of the administration of MLN0128 ([Table 8-1](#)).

**Table 8-1 Definition of Dose-Limiting Toxicity**

- 
- Grade  $\geq 3$  non hematologic toxicity, except for
    - 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);
    - Grade 3 hyperglycemia lasting  $\leq 14$  days (all subjects should receive optimal antiglycemic treatment, including insulin);
    - Grade 3 rash lasting  $\leq 3$  days (all subjects should receive topical steroid treatment, oral antihistamines, and pulse oral steroids, if necessary).
  - Grade 4 neutropenia lasting  $> 7$  days in the absence of growth factor support.
  - Grade 4 neutropenia of any duration accompanied with fever  $\geq 38.5^{\circ}\text{C}$  and/or systemic infection.
  - Any other Grade  $\geq 4$  hematologic toxicity.
  - Inability to administer at least 75% of planned 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  $\leq 1$  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 MLN0128 at a  $\geq 25\%$  dose reduction (or next lower dose level) with approval of the

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sponsor's medical monitor. See Section 8.6 for management of MLN0128 dose for specific clinical events.

#### 8.2.2 Dose Escalation Plan to Determine the Maximum Tolerated Dose

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

The initial dose escalation started with the once-daily dosing schedule in subjects with advanced solid malignancies, and the MTD<sup>qd</sup> has been determined to be 6 mg QD. Upon implementation of Amendment 7, enrollment was initiated and is ongoing to evaluate 2 alternate dosing schedules: Arm A with QW dosing starting at a dose not to exceed that of twice the MTD<sup>qd</sup> and Arm B with MLN0128 administered QD×3d QW starting at the MTD<sup>qd</sup>. Amendment 10 added a further dosing arm, Arm C, where study drug is administered QD×5d QW starting at a dose not to exceed the total weekly dose of the MTD<sup>qd</sup> ( $\leq 42$  mg/week). Initial dose cohorts for each of the alternate dosing schedules (Arms A, B) prior to Amendment 10 enrolled a single subject. If Grade  $\geq 2$  AE, regardless of relatedness to MLN0128, is observed in any single subject cohort, an additional 2 to 5 subjects will be assigned to that cohort and subsequent dose cohorts in that arm will include 3 to 6 subjects as previously described. Upon implementation of Amendment 10, Arm C will enroll 3 subjects, with an additional 3 subjects enrolled should a DLT be observed per standard 3 + 3 phase 1 cohort design. Subjects will be randomly assigned to each of the 3 alternate dosing arms should 2 or more arms be open for enrollment at the same time.

Dose escalation will only proceed if no DLT is observed in a cohort of at least 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.

A summary of the dose escalation decision rules for MTD determination is provided in [Table 8-2](#).

**Table 8-2 Maximum Tolerated Dose Determination and Cohort Expansion**

<b>Number of Subjects with DLT<sup>a</sup></b>	<b>Dose Escalation Decision Rule</b>
0 of 3	Enter 3 subjects at the next dose level.
1 of 3	Enter up to 3 more subjects at this dose level. <ul style="list-style-type: none"> <li>• If none of the 3 additional subjects has a DLT, proceed to the next dose level.</li> <li>• If 1 or more of the 3 additional subjects has a DLT, then dose escalation will be stopped, and the MTD has 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.</li> </ul>
≥ 2	Stop dose escalation. MTD may have been exceeded. <ul style="list-style-type: none"> <li>• 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 or a lower level may be evaluated.</li> </ul>
≤ 1 of 6 at the highest evaluated dose level	This is usually the MTD.

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

a Number of subjects per cohort with a DLT during Cycle 1 (Days 1 - 28).

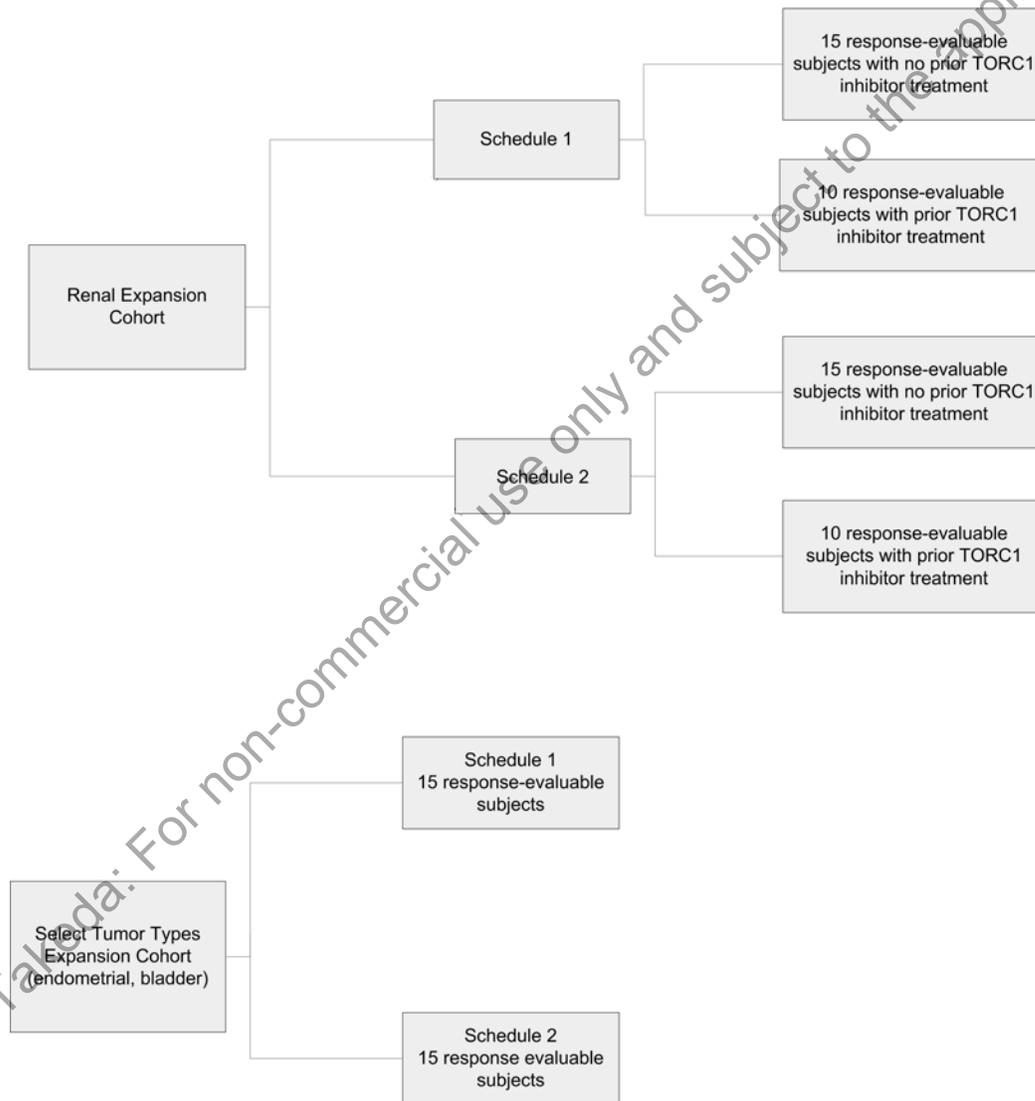
The MTD determination for each of the 4 dosing schedules evaluated will be based on initial cohorts of 6 evaluable subjects each as described in [Table 8-2](#). Once the MTD has been identified for each of the 4 dosing schedules, an additional 6 subjects may be enrolled at the MTD of each dosing schedule to gain more PK and safety data before the expansion phase of the study. The safety and tolerability data from all subjects enrolled at a given dose and schedule will be evaluated to determine the recommended dose(s) and schedule(s), based on the totality of safety data, for further study in the expansion phase.

All participating sites are required to send in DLT notification forms within 24 hours of learning of the event (details will be provided in the Study Reference Manual). All DLT(s) 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 each cohort. Participating investigators and the sponsor's medical monitor will review study toxicities from the current cohort during the site teleconferences before escalating to the next dose level, de-escalating to an intermediate dose level, or adding additional subjects at the current dose level.

### 8.3 Expansion Phase

After the MTD has been determined for each of the dosing schedules in the dose escalation phase, based on the evaluation of biochemical, PK, and tolerability data, and potentially early signs of antitumor activity, 1 or more of these schedules (initially 2) will be advanced in the expansion phase for study in 2 cohorts, a renal cancer cohort and a cohort of selected tumor types (endometrial and bladder cancers). As shown in Figure 8-1, approximately 15 to 25 response-evaluable subjects per treatment schedule will be enrolled into each cohort.

**Figure 8-1 Expansion Stage Cohort Enrollment**



Subjects who receive at least 1 dose of MLN0128, have measurable disease at baseline, and undergo at least 1 postbaseline disease assessment are considered response-evaluable.

#### **8.4 Intrasubject Dose Escalation**

Once the MTD is determined for each dosing schedule (QD, QW, QD×3d QW, and QD×5d QW) of single-agent MLN0128, intrasubject dose escalation within a given dosing schedule may be allowed (at the investigator's discretion and with the sponsor's approval) in subjects actively receiving single-agent MLN0128 at a dose lower than the MTD and for a minimum of 8 weeks in the absence of disease progression or unacceptable treatment-related toxicity. Subjects may not switch from 1 dosing schedule to another or participate in more than 1 dosing schedule arm at any time.

#### **8.5 Dose Modification or Treatment Delay for MLN0128-related Toxicity**

MLN0128 dosing should be withheld for  $\geq$  Grade 3 MLN0128-related toxicities. If the event resolves to Grade  $\leq$  1 or baseline values within 28 days of interrupting therapy, the subject may resume study treatment at a  $\geq$  25% dose reduction or, for subjects in the dose escalation phase, at the next lower dose level with the sponsor's approval. If dose modification is required for subjects receiving  $\leq$  4 mg QD, then the dosing frequency should be decreased to 5 days per week, instead of decreasing the daily dose administered. If MLN0128 dosing is delayed for  $>$  28 consecutive days for MLN0128-related toxicity despite supportive treatment per standard clinical practice or more than 2 dose reductions of MLN0128 is required in a subject, stop MLN0128 therapy, discontinue the subject from the study, and complete the follow-up visit within 30 days of the last administration of MLN0128.

See Section 8.6 for management of MLN0128 dosing for specific clinical events.

The sponsor's medical monitor should be contacted prior to any dose modification in MLN0128 for any subject in the study.

#### **8.6 Management of Clinical Events**

##### **8.6.1 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 predose fasting blood glucose (FBG) levels at home. Subjects will be instructed to notify the study staff immediately with any abnormal readings (ie,  $\geq$  150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no

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irregularities in the fasting blood glucose level are observed during a minimum of 6 consecutive months, then the frequency of in-home fasting glucose testing may be reduced to twice weekly if the investigator approves. Subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL and, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of fasting blood glucose levels will be reinstated to daily.

Guidance for MLN0128 dose management in the event of hyperglycemia is provided in [Table 8-3](#).

**Table 8-3 Management of Hyperglycemia**

<b>Grade</b>	<b>Description</b>	<b>Treatment</b>	<b>MLN0128 Dose Modification</b>
1	Fasting blood sugar > ULN–160 mg/dL	Continue close monitoring of blood sugars. Initiate oral hypoglycemic agent.	None.
2	Fasting blood sugar > 160–250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None.
≥3	Fasting blood sugar > 250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤ Grade 2. Resume MLN0128 based on timing of recovery: ≤ 1 week: resume at same dose and schedule; >1 but ≤ 2 weeks: reduce by 25% <sup>a</sup> ; > 2 weeks: stop MLN0128 and discontinue subject from the study.

**Prevention/Prophylaxis**

- Follow fasting serum glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Life-style modifications, as appropriate (balanced diet, limit alcohol consumption, increase physical activity).
- Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin.
- Early initiation of therapy is recommended to prevent higher grade hyperglycemia.
- Fasting blood glucose levels ≥ 150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.

Abbreviations: dL = deciliters; mg = milligrams; ULN = upper limit of normal.

a If dose modification is required for subjects receiving ≤ 4 mg QD, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

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In the event that any FSG reading performed at the site indicates hyperglycemia ( $>$  upper limit of normal [ULN] or  $\geq 110$  mg/dL), 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), had continued to take their concomitant antiglycemic medications should the subject have underlying diabetes mellitus, 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.

Based on the clinical experience from MLN0128 trials, most episodes of hyperglycemia observed have been Grade 1 or 2 that have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since instituting a standard regimen for early treatment of hyperglycemia. All subjects developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of subjects who develop Grade 1 hyperglycemia (FSG  $>$  ULN  $\leq 160$  mg/dL) or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as metformin. All subjects with Grade  $\geq 2$  hyperglycemia (FSG  $> 160$  mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated while continuing on MLN0128. The investigator should consult an endocrinologist if needed to aid in optimizing the subject's hyperglycemia treatment plan.

It is recommended that subjects be treated initially with a fast acting, insulin sensitizer, such as metformin at 500 mg PO QD, and titrate up to a maximum of 1000 mg PO BID as needed. Concurrent addition to metformin of 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.

#### **8.6.2 Management of Noninfectious Pneumonitis**

Guidance for MLN0128 dose management in the event of noninfectious pneumonitis is shown in [Table 8-4](#). Noninfectious pneumonitis has not been observed with MLN0128 as of December 2012.

**Table 8-4 Management of Non-infectious Pneumonitis**

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic: Radiographic findings only	Rule out infection and closely monitor.	None.
2	Symptomatic: Not interfering with ADLs	Rule out infection and consider treatment with corticosteroids until symptoms improve to $\leq$ Grade 1.	Interrupt MLN0128 treatment: When symptoms $\leq$ Grade 1, re-initiate MLN0128 treatment with a 25% dose reduction <sup>a</sup> . Discontinue MLN0128 treatment if failure to recover within 4 weeks.
3	Symptomatic: Interfering with ADLs; Requires administration of O <sub>2</sub>	Rule out infection and consider treatment with corticosteroids until symptoms improve to $\leq$ Grade 1.	Interrupt MLN0128 treatment until symptoms resolve to $\leq$ Grade 1. Consider re-initiating MLN0128 treatment with a 25% dose reduction <sup>a</sup> . If toxicity recurs at Grade 3, discontinue MLN0128 treatment.
4	Life-threatening: Ventilatory support indicated	Rule out infection and consider treatment with corticosteroids.	Discontinue MLN0128 treatment.

Abbreviations: ADL = activities of daily living ; O<sub>2</sub> = oxygen gas.

a If dose modification is required for subjects receiving  $\leq$  4 mg QD, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

### 8.6.3 Management of Hyperlipidemia

Guidance for MLN0128 dose management in the event of hyperlipidemia is shown in [Table 8-5](#).

**Table 8-5 Management of Hyperlipidemia**

Grade	Description	Treatment	MLN0128 Dose Modification
1	Cholesterol: > ULN - 300 mg/dL Triglycerides: > 150 - 300 mg/dL	None.	None.
2	Cholesterol: > 300 – 400 mg/dL Triglycerides: > 300 - 500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides $\geq$ 500 mg/dl should be treated urgently due to risk of pancreatitis.	Maintain dose if tolerable.  If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to $\leq$ Grade 1. Reinitiate at same dose.

**Table 8-5 Management of Hyperlipidemia**

Grade	Description	Treatment	MLN0128 Dose Modification
3	Cholesterol: > 400 - 500 mg/dL Triglycerides: > 500 - 1000 mg/dL	Same as for Grade 2.	Hold dose until recovery to ≤ Grade 1, then restart with a 25% dose reduction <sup>a</sup> .
4	Cholesterol: > 500 mg/dL Triglycerides: > 1000 mg/dL	Same as for Grade 2.	Discontinue treatment.

**Prevention/Prophylaxis**

- Life-style modifications, as appropriate (balanced diet, limit consumption of alcoholic beverages, increase physical activity).

Abbreviations: dL = deciliters; mg = milligrams; ULN = upper limit of normal.

- a If dose modification is required for subjects receiving ≤ 4 mg QD, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

**8.6.4 Management of Oral Mucositis**

Guidance for MLN0128 dose management in the event of oral mucositis is provided in [Table 8-6](#).

**Table 8-6 Management of Oral Mucositis**

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic or mild symptoms	Non-alcoholic mouth wash or 0.9% salt water rinse; Consider topical corticosteroids at earliest signs of mucositis.	None.
2	Moderate pain, not interfering with oral intake  Modified diet indicated	Topical analgesic mouth treatments; Topical corticosteroids; Initiate antiviral or antifungal therapy, if indicated.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Severe pain, interfering with oral intake	Same as for Grade 2; Consider intra-lesional corticosteroids.	Hold dose until recovery to ≤ Grade 1, then restart with a 25% dose reduction <sup>a</sup> .
4	Life-threatening consequences	Same as for Grade 2. Consider intra-lesional corticosteroids.	Discontinue treatment.

**Prevention/Prophylaxis**

- Consider initiation of a non- alcoholic mouth wash or 0.9% salt water rinses 4-6 times daily with start of therapy before signs of mucositis develop.

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- Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

a If dose modification is required for subjects receiving  $\leq 4$  mg QD, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

#### 8.6.5 Management of Rash

Guidance for MLN0128 dose adjustment for the event of rash is provided in [Table 8-7](#).

**Table 8-7 Management of Rash**

Grade	Description	Treatment	MLN0128 Dose Modification
$\leq 2$	Macules/papules covering $\leq 30\%$ body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment and/or oral anti-histamines.	None.
$\geq 3$	Macules/papules covering $> 30\%$ body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment, oral anti-histamines, and/or pulsed steroids.	Hold until $\leq$ Grade 2; Resume MLN0128 based on timing of recovery: $\leq 2$ weeks: reduce dose by 25% <sup>a</sup> ; $> 2$ weeks: stop MLN0128 and discontinue subject from the study.

a If dose modification is required for subjects receiving  $\leq 4$  mg QD, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

#### 8.6.6 Management of Nausea and/or Vomiting

Guidance for MLN0128 dose adjustment for the event of nausea and/or vomiting is provided in [Table 8-8](#).

**Table 8-8 Management of Nausea and/or Vomiting**

Grade	Description	Treatment	MLN0128 Dose Modification
$\leq 2$	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; Consider IV fluid hydration.	None.
$\geq 3$	Inadequate oral intake; $\geq 6$ episodes of vomiting within 24 hours	Maximize anti-emetic therapy; Initiate tube feeding, IVF, or TPN.	Hold until $\leq$ Grade 1; Resume MLN0128 without dose modification.

#### Prevention/Prophylaxis

Prophylactic use of anti-emetic, anti-nausea, and anti-diarrheal medications are encouraged and may be used before each dose of MLN0128 as needed throughout the study.

Abbreviations: IV = intravenous; IVF = intravenous fluids; TPN = total parenteral nutrition

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#### 8.6.7 Management of Cardiac Events

##### 8.6.7.1 Management of Cardiac Instability

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

##### 8.6.7.2 Management of Left Ventricular Dysfunction

Guidance for MLN0128 dose adjustment for the event of left ventricular dysfunction is provided in [Table 8-9](#).

**Table 8-9 Management of Left Ventricular Dysfunction**

Grade	Description	MLN0128 Dose Modification
1	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.
≥ 2	Symptomatic cardiac dysfunction/congestive heart failure	Discontinue treatment.

Abbreviations: LLN = lower limit of normal; LVEF = left ventricular ejection fraction.

##### 8.6.7.3 Management of QTc Prolongation

Guidance for MLN0128 dose adjustment for the event of QTc prolongation is provided in [Table 8-10](#).

**Table 8-10 Management of QTc Prolongation**

Grade	Description	Treatment	MLN0128 Dose Modification
2	480 msec < QTc < 501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication, etc.)	None; continue MLN0128 at the same dose and schedule.
≥ 3	QTc ≥ 501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication) <sup>a</sup> ; Consider a formal consult by a cardiologist; Notify the sponsor's medical monitor; Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.	MLN0128 should be interrupted.  The decision whether to reinitiate MLN0128 treatment with or without dose reduction and additional monitoring in those subjects who had asymptomatic prolonged QTc ≥ 501 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.

Abbreviations: ECG = electrocardiogram; IV = intravenous; msec = milliseconds; QTc = QT interval corrected for heart rate

a A list of medications known to prolong QTc can be found at [www.torsades.org](http://www.torsades.org) and [www.QTdrugs.org](http://www.QTdrugs.org).

#### 8.6.7.3.1 Acquisition of 12-Lead Electrocardiograms

All scheduled ECGs should be performed after the subject 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.

#### 8.6.7.3.2 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; See [Table 8-10](#)). A list of medications known to prolong QTc can be found at [torsades.org](http://torsades.org) and [QTdrugs.org](http://QTdrugs.org). If done prior to protocol enrollment and if a repeat ECG meets eligibility requirements, the subject may enroll in the study upon review and agreement by the medical monitor.

### 8.6.8 Management of Other Nonhematologic Toxicities

Guidance for MLN0128 dose management in the event of nonhematologic toxicities is shown in Table 8-11.

**Table 8-11 Management of Other Nonhematologic Toxicities (including asthenia/weakness)**

Grade	Description	Treatment	MLN0128 Dose Modification
1	Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated		If tolerable, no adjustment required.
2	Moderate: minimal, local, or non-invasive intervention indicated	Initiate appropriate medical therapy and monitor.	If tolerable, no adjustment required. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to $\leq$ Grade 1. Reinitiate at same dose level. If toxicity recurs at Grade 2, interrupt MLN0128 dosing until recovery to $\leq$ Grade 1. Reinitiate with a 25% dose reduction <sup>a</sup> .
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated		Interrupt MLN0128 treatment until symptoms resolve to $\leq$ Grade 1. Re-initiate MLN0128 treatment with a 25% dose reduction <sup>a</sup> . If toxicity recurs at Grade 3, discontinue MLN0128 treatment.
4	Life-threatening consequences – urgent intervention required		Discontinue MLN0128 treatment.

a If dose modification is required for subjects receiving  $\leq$  4 mg QD, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

## 8.7 Discussion of Study Design, Including Choice of Control Group

The proposed study design is consistent with other first-in-human oncology trials that assess safety and tolerability. Neither a placebo nor an active control is included in this study.

## 8.8 Selection of Study Population

### 8.8.1 Inclusion Criteria

*Individuals eligible to participate in either the dose escalation phase and/or the expansion phase of the study must meet all the following Inclusion Criteria:*

1. Age  $\geq$  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 standard of care therapy. Subjects with locally advanced or metastatic solid tumors who have 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, they 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. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1;
4. Subjects must have adequate organ function, including the following:
  - a. Bone marrow reserve consistent with absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$ ; platelet count  $\geq 100 \times 10^9/L$  hemoglobin  $\geq 9$  g/dL;
  - b. Hepatic: total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT)  $\leq 2.5 \times$  ULN ( $\leq 5 \times$  ULN if liver metastases are present);
  - c. Renal: creatinine clearance  $\geq 50$  mL/min based either on Cockcroft-Gault estimate or based on urine collection (12 or 24 hour);
  - d. Metabolic: fasting serum glucose ( $\leq 130$  mg/dL) and fasting triglycerides  $\leq 300$  mg/dL;
5. Left ventricular ejection fraction (LVEF) within 5 absolute percentage points of 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);
6. 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;

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7. 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;
8. Willingness to provide paraffin blocks or a minimum of 10 unstained slides of available archival tumor tissues (paraffin blocks are preferred);
9. Ability to swallow oral medications;
10. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures;

Subjects who have tumor tissue that is accessible for biopsy based on the investigator's judgment will be strongly encouraged to consent for tumor biopsy.

*Additionally, for individuals eligible to participate in the expansion phase of the study:*

11. Subjects must have evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1<sup>(1)</sup> by radiographic techniques (computerized tomography [CT] or magnetic resonance imaging [MRI]);
12. Subjects must have a pathologic diagnosis of advanced or recurrent endometrial adenocarcinoma and must have failed at least 1 prior line of standard chemotherapy; or
13. Subjects must have a pathologic diagnosis of advanced/metastatic urothelial cancer (carcinoma of the bladder, ureter, and/or renal pelvis) and must have failed at least 1 line of prior therapy in the metastatic/unresectable setting; or
14. Subjects must have a pathologic diagnosis of advanced renal cell carcinoma (RCC) and must have failed at least 1 prior line of anti-VEGF therapy (including but not limited to sunitinib, and/or sorafenib, and/or bevacizumab and/or pazopanib, and/or axitinib) and must not have received prior therapy with a TORC1 inhibitor (such as temsirolimus or everolimus); or
15. Subjects must have a pathologic diagnosis of advanced renal cell carcinoma (RCC) and must have progressed on treatment with a TORC1 inhibitor (such as temsirolimus or everolimus).

### 8.8.2 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. Untreated brain metastasis or history of leptomeningeal disease or spinal cord compression;
3. Failed to recover from the reversible effects of prior anticancer therapies, with the exception of, alopecia, and after-effects associated with prior tyrosine kinase inhibitor therapy, such as hair depigmentation, hypothyroidism, and/or splinter hemorrhage;
4. 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 equal 28 days prior to the first administration of study drug, and the subject must have documented disease progression;
5. Have received systemic corticosteroid (inhalers are allowed) within 1 week prior to the first administration of study drug (dose escalation phase only);
6. Have initiated treatment with bisphosphonates less than 30 days prior to the first administration of MLN0128. Concurrent bisphosphonate use is only allowed if the bisphosphonate was initiated at least 30 days prior to the first administration of MLN0128;
7. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128;
8. 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;
9. Other clinically significant comorbidities, such as uncontrolled pulmonary disease, active CNS disease, active infection, or any other condition that could compromise subject's participation in the study;
10. Known human immunodeficiency virus (HIV) infection;

11. Pregnancy (positive serum or urine pregnancy test) or breast feeding;
12. Any history of unstable angina, myocardial infarction, New York Heart Association (NYHA) Class III or IV heart failure (See [Table 21-3](#)), and/or pulmonary hypertension;
13. 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/transient ischemic attack within 6 months prior to enrollment.
14. A requirement for positive inotropic support (excluding digoxin) or active/serious uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation) within 1 year prior to screening;
15. A pacemaker or implantable cardiac defibrillator;
16. Baseline prolongation of the rate-corrected QT interval (QTc) (eg, repeated demonstration of QTc interval > 480 milliseconds) (See [Section 8.6.7.3.2](#));
17. History of congenital long QT syndrome, ventricular fibrillation, ventricular tachycardia, or torsades de pointes;
18. Diagnosed or treated for another malignancy within 2 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection;

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19. Additionally, for individuals eligible to participate in the expansion phase of the study, subjects will be excluded if they have received prior AKT, PI3K, dual PI3K/mTOR complex (TORC1/2), or TORC1/2 inhibitors.

Other considerations for exclusion: Subjects taking moderate/strong CYP1A2 inhibitors, moderate CYP1A2 and/or strong and moderate CYP3A4 inducers should be considered with caution. Alternative treatments that are less likely to affect MLN0128 metabolism, if available, should be considered. If a subject requires treatment with 1 or more moderate/strong CYP1A2 inhibitor, a moderate/strong CYP1A2 and/or a strong CYP3A4 inducer, the medical monitor should be consulted. Examples of clinically relevant moderate/strong CYP1A2 inhibitors and inducers, as well as strong CYP3A4 inducers, are presented in Table 21.2.

#### 8.8.3 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. Also, Millennium 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  $\leq$  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 the study drug. 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 Institutional Review Board (IRB)/Ethics Committee (EC) 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 Health Insurance Portability and Accountability Act (HIPAA) in the US, and Organic Law 15/1999 of 13 December 1999 on the Protection of Personal Data in Spain, 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.

#### 8.8.4 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. This unique identifier will be on all Case Report Form (CRF) pages. During dose escalation, subjects who discontinue treatment before completing  $\geq 75\%$  (21 of 28 for QD dosing schedule; 9 of 12 for QD $\times$ 3d

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QW, and 15 of 20 for QD×5d QW dosing schedules; or 3 of 4 for QW dosing schedule) of planned MLN0128 doses during Cycle 1 for reasons other than study drug-related toxicity will be replaced. During expansion, subjects who receive less than 75% of MLN0128 doses during Cycles 1 and 2 will not be replaced if they discontinue due to either disease progression or unacceptable toxicity.

## **8.9 Treatments**

### **8.9.1 Treatments Administered**

Subjects will receive MLN0128 as monotherapy in this study. In the absence of unacceptable MLN0128 treatment-related toxicity or disease progression, subjects may receive MLN0128 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. Millennium and its designee will provide the study site with a supply of MLN0128 sufficient for the completion of the study.

### **8.9.2 Identity of Investigational Product**

MLN0128 is a small molecule being developed as a potent, selective inhibitor of TORC1/2 for the treatment of subjects with advanced malignancies, including NHL, and hematologic malignancies.

#### **8.9.2.1 Product Characteristics**

MLN0128 will be supplied in tamper-resistant bottles as capsules containing 1 of 3 dose strengths.

- MLN0128 capsules, 1 mg;
- MLN0128 capsules, 3 mg; and/or
- MLN0128 capsules, 5 mg;

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

### **8.9.3 Storage and Labeling**

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

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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 designated drug handler will inventory MLN0128 (separately for each strength) 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°C to 30°C (59°F 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.

#### **8.9.4 Directions for Administration**

MLN0128 will be administered orally once in the morning with a meal at approximately the same time of day. Subjects should be encouraged to drink at least 18 to 24 ounces (oz) of liquids a day to stay well-hydrated. Cycles are repeated every 28 days.

- QD dosing schedule: once daily in the morning on Days 1 through 28 of each cycle;
- QW dosing schedule: once in the morning on Days 1, 8, 15, and 22 of each cycle;
- QD×3d QW dosing schedule: once in the morning on Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24 of each cycle;
- QD×5d QW dosing schedule: once in the morning on Days 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, and 26 of each cycle.

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). 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. Additional details will be provided in the Pharmacy Manual.

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Subjects should not have anything by mouth (eat or drink) except water and/or medications after midnight or a minimum of 8 hours prior to their clinic visits when blood draws for fasting glucose or fasting lipid profile will be required. The investigator may consider hydrating subjects as clinically indicated with 500 mL IV Normal Saline (NS) solution pre- and/or post- MLN0128 dosing on clinic days to minimize risk of dehydration, especially in fasting subjects, and subsequent prerenal azotemia.

MLN0128 capsules should not be opened or crushed. 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). 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.

Prophylactic use of anti-emetic, anti-nausea, and anti-diarrheal medications are encouraged and may be used prior to each MLN0128 dosing as needed throughout the study.

#### **8.9.5 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 9.2.

#### **8.9.6 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 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. In the event, that more than 1 dosing arm is open for enrollment during the dose escalation or expansion phases, then subjects will be assigned to a dose schedule in an alternating basis. Subjects may not participate in more than 1 dosing arm.

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Sites cannot enroll or start dosing the subject without receiving the assigned subject number and treatment cohort from Millennium or its designee.

#### 8.9.7 Selection of Doses Used in the Study

The starting dose for the daily dosing schedule is 2 mg once daily.

The  $STD_{10}$  has been defined as 3 mg/kg/day (18 mg/m<sup>2</sup>/day) and the HNSTD in monkeys as 0.15 mg/kg/day (1.8 mg/m<sup>2</sup>/day). Using the FDA endorsed paradigm for selecting the maximum starting dose in humans, 1-tenth the rodent  $STD_{10}$  (ie, 1.8 mg/m<sup>2</sup>/day) was compared to the HNSTD in monkeys.<sup>(26)</sup> Since 1/10th the  $STD_{10}$  in the rat was not severely toxic to the monkey, 1/10th the  $STD_{10}$  in rats can be used as the maximum human starting dose. A maximum human starting dose of 1.8 mg/m<sup>2</sup>/day for an average sized subject of 1.7 m<sup>2</sup> is calculated as 3 mg/day. Recognizing that prior human experience does not exist with MLN0128 and allometric scaling predicts a potential for drug accumulation in humans at steady state, Millennium proposes the human starting dose be 2 mg/day (1.2 mg/m<sup>2</sup>/day). Based on preclinical data, it is estimated that a dose of 2 mg/day in humans could achieve systemic exposures sufficient for biological inhibition of target. Thus, this starting dose should offer an opportunity for potential therapeutic benefit while minimizing subject's risk.

The starting doses of the additional dosing schedules to be evaluated will be based on the MTD of the QD dosing schedule (MTD<sup>qd</sup>). Arm A, with once-weekly dosing, will start at a dose not to exceed that of twice the MTD<sup>qd</sup>. Arm B, with MLN0128 being administered QD×3d QW, will start at the MTD<sup>qd</sup>; Arm C, with MLN0128 QD×5d QW, will start at a dose not to exceed the total weekly dose of the MTD<sup>qd</sup> (ie, ≤ 42 mg/week). Dose escalation for the dosing schedules will be according to a modified Fibonacci schema. For example, the starting dose of 2 mg may be escalated in successive cohorts to 4 mg, 7 mg, 10 mg, 14 mg, 18 mg, or an intermediate dose between 2 planned doses may be evaluated. The level of dose escalation will be determined after review of available safety data and discussion between the participating Investigators and Millennium's medical monitor prior to the dose escalation, but the dose selected will not exceed the planned dose according to a modified Fibonacci schema.

##### 8.9.7.1 Selection of Timing of Dose for Each Subject

It is anticipated that MLN0128 will possess a plasma half-life commensurate with once daily administration in humans. Preclinical models of efficacy, safety, and PK have largely relied on once-daily dosing. Investigation of different dosing schedules in preclinical efficacy models has demonstrated commensurate tumor growth inhibition with administration of

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MLN0128 either once daily, twice daily, or intermittently (eg, once every other day or weekly).

#### **8.9.8 Blinding**

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

#### **8.9.9 Prior and Concomitant Medications**

All prescription and over-the-counter medications, including influenza vaccines, 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 chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation or surgery (subjects can have palliative radiation or surgery in the study for pre-existing lesions)
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers) 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
- Moderate and strong cytochrome CYP1A2 inhibitors and moderate and strong CYP1A2 and CYP3A4 inducers should be administered with caution and at the discretion of the investigator.

Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications are encouraged and may be used prior to first dose of study drug (MLN0128), and as needed throughout the study prior to each dosing and as clinically indicated per standard practice. Initiation of hematopoietic growth factors, transfusions of blood, and blood products should not be used in the first cycle during the dose escalation phase unless absolutely clinically necessary and after discussion with Millennium's medical monitor. However, they may be administered after Cycle 1 if needed. Subjects who have been on chronic erythropoietin for  $\geq 30$  days may continue to receive the concomitant medication upon study entry.

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Concurrent bisphosphonate use is only allowed if the bisphosphonate was initiated at least 30 days 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.

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.

#### **8.9.10 Treatment Compliance**

The importance of treatment compliance should be emphasized to the subject. Subjects will be given study drug and 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 schedule will be assessed by reconciliation of the used and unused study drug at each clinic visit and review of the dosing diaries. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided for the study. Compliance will be monitored and documented by site personnel on the appropriate form. The site personnel will question the subject regarding adherence to the dosing schedule by reviewing the dosing diaries, recording the number of capsules and strengths returned, the date returned, and determining treatment compliance before dispensing new medication to the study subject.

#### **8.10 Investigational Product Accountability**

The principal investigator (PI) or designee is responsible for maintaining accurate records (including dates and quantities) of investigational product (IP) 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 Clinical Research Associate (CRA) has confirmed the accountability data.

##### **8.10.1 Return and Disposition of Clinical Supplies**

Unused study drug must be kept in a secure location for accountability and reconciliation by the Millennium-designated CRA. The investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

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. The

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Millennium-designated CRA must account for all study drug in a formal reconciliation process before destroying study drug. 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 accounted for on a Study Drug Return Form 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.

#### **8.11 Dietary or Other Protocol Restrictions**

No dietary restrictions will be imposed on study subjects.

#### **8.12 Efficacy and Safety Variables**

See the [Schedule of Events](#) for timing of evaluations.

##### **8.12.1 Safety Variables**

Safety will be assessed by periodic physical examinations, 12-lead electrocardiograms (ECGs; see Sections [8.6.7.3.1](#) and [8.6.7.3.2](#)), 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 NCI CTCAE version 4.0.

##### **8.12.2 Efficacy Variables**

Radiographic and/or physical assessments of the malignancies, and evaluations of relevant tumor markers (eg, cancer antigen 125 [CA125], prostate-specific antigen (PSA), cancer

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antigen 19-9 [CA19-9], CA27.29, CA15.3, and carcinoembryonic antigen [CEA]) will be made at screening/baseline (within 28 days before the first study drug administration) and after every 2 cycles of treatment (or up to every 4 cycles for long-term patients, defined as study participation  $\geq$  3 years). 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. Response will be assessed using RECIST version 1.1. A confirmatory CT/MRI scan should be performed at approximately 4 weeks from the previous scan for all subjects with an objective response of  $\geq$  PR.

#### 8.12.3 Additional Variables

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 the study drug in plasma. The pharmacodynamic effect of MLN0128 activity in surrogate tissue (skin and tumor tissue) via 4EBP1, AKT, and S6 as well as 4EBP1 in peripheral blood cells (dose escalation phase only) and correlation of somatic mutations (PI3KCA, PTEN, Ras) in archival paraffin tumor tissue with MLN0128 activity will be evaluated. CCI

Additionally, duration of a subject on MLN0128 versus the duration of the same subject on the last systemic anticancer therapy that is not an investigational agent prior to entering the study will be explored.

## 9. ADVERSE EVENTS

### 9.1 Definitions

#### 9.1.1 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.

#### 9.1.2 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.

#### 9.1.3 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.<sup>(27)</sup> 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<sup>3</sup> 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.

## 9.2 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 9.3 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 9.1) must be reported (see Section 9.3 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 yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

### **9.3 Monitoring of Adverse Events and Period of Observation**

AEs, both non-serious 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).

#### **9.4 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 9.2). 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 9.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

## 10. APPROPRIATENESS OF MEASUREMENTS

### 10.1 Pharmacokinetics

The plasma concentrations for MLN0128 will be determined using a liquid chromatography tandem mass spectrometry method. The measured MLN0128 plasma concentrations will be used to determine the PK parameters, including AUC,  $C_{max}$ ,  $C_{min}$ ,  $T_{max}$ , and  $t_{1/2}$ . 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.

### 10.2 Biomarker Assessments

#### 10.2.1 Pharmacodynamic Assessments

During the dose escalation phase, pharmacodynamic assessment will be made by assessing various biomarker levels in samplings of peripheral blood cells (PBCs), skin and tumor biopsies pre- and post-treatment whenever possible. The PD effect of MLN0128 activity in surrogate tissue (skin and tumor tissue) via 4EBP1, AKT, and S6 as well as peripheral blood cells (dose escalation only) via 4EBP1 will be evaluated. CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The afore mentioned biomarkers are downstream effectors of mTOR and have been used for determining the sensitivity of proliferative diseases to treatment with mTOR inhibitors. The changes in biomarkers levels will be determined via flow cytometry and/or immunohistochemical analysis. The absolute and percent change from baseline will be calculated for each subsequent measurement. Summary statistics will be computed for each collection time point.

#### 10.2.2 Assessments of Predictive Markers of MLN0128 Activity

Candidate somatic genetic markers that may predict MLN0128 activity will be evaluated in archival tumor tissues. These include PI3KCA, PTEN, Ras (K/H/N) in archival paraffin tumor tissue with MLN0128 activity.

CCI [REDACTED]

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**11. STUDY PROCEDURES**

See the [Schedule of Events](#) for the timing of all study-related procedures.

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**12. 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.

**12.1 Analysis Endpoints**

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

**12.1.1 Primary Endpoints****12.1.1.1 Dose Escalation Phase**

The maximum tolerated dose of MLN0128 when administered orally daily as monotherapy in subjects with advanced solid malignancies will be determined. The MTD is defined as the highest dose level of MLN0128 at which no more than 1 out of 6 evaluable subjects experience a DLT during the first cycle (28 days) of therapy. The rate of DLT in each cohort will be determined from the occurrence of AEs which meet the criteria in Section 8.2.1. Once the MTD for daily administration of MLN0128 has been determined, the MTD for alternate dosing schedules of MLN0128 will be evaluated.

**12.1.1.2 Expansion Phase**

The objective response rate will be estimated for subject. The objective response rate is based on the subject's best overall tumor response documented during the course of MLN0128 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. In addition, the duration of stable disease will be evaluated for subjects with the best response of stable disease.

**12.1.2 Secondary Endpoints**

The pharmacokinetics of daily and alternate schedule dosing of MLN0128 will be determined from selected subjects based on the PK parameters listed below. Serum samples

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for PK analysis will be collected at the time points specified in the [Schedule of Events](#) and in the PK Sampling Scheme in [Table 3-5](#).

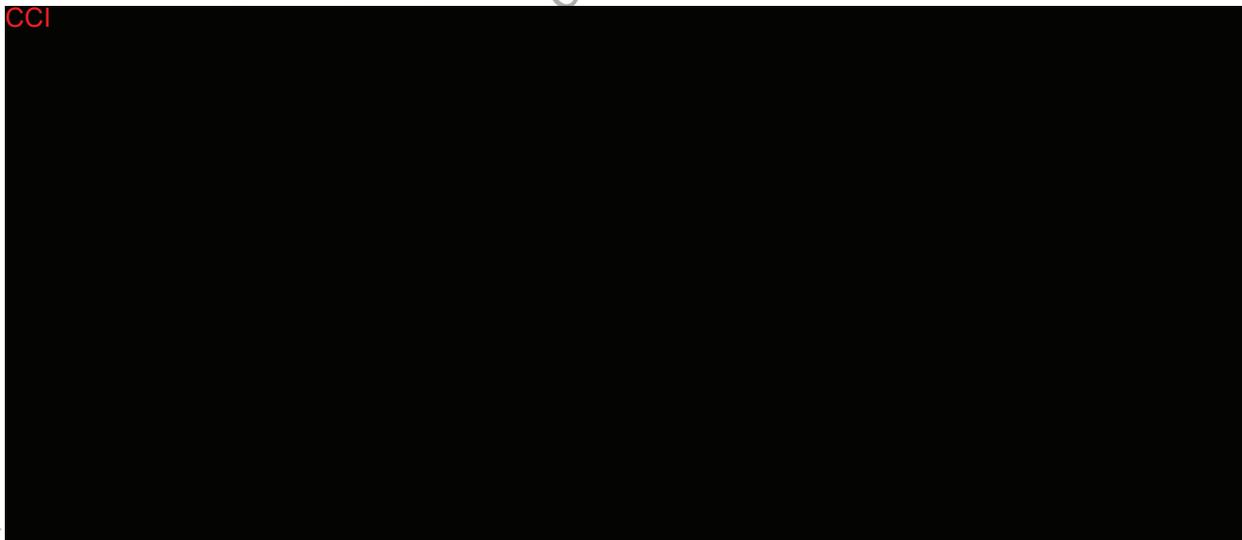
- Maximum plasma concentration ( $C_{max}$ );
- Minimum plasma concentration ( $C_{min}$ );
- Time of maximum plasma concentration ( $T_{max}$ );
- Plasma half-life ( $t_{1/2}$ );
- Area under the plasma concentration-time curve from time zero to infinity ( $AUC_{0-\infty}$ ), zero to last dose ( $AUC_{0-last}$ ), and %AUC extrapolated;

The PD effect of MLN0128 activity in surrogate tissue (skin and tumor tissue) via 4EBP1, AKT, and S6 as well as peripheral blood cells via 4EBP1 will be evaluated.

- Change from baseline in the levels of 4EBP1 and S6 in skin and tumor tissues as well as 4EBP1 in peripheral blood cells.

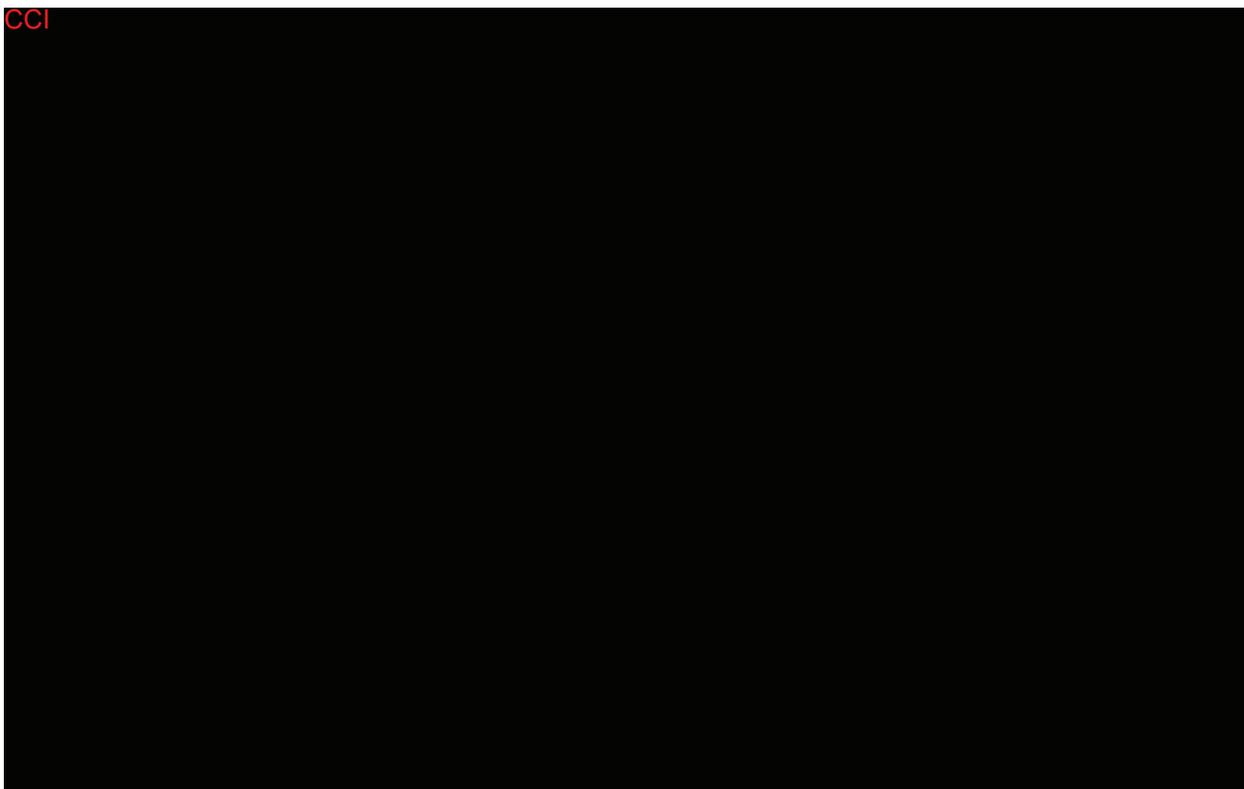
#### 12.1.3 Exploratory Endpoints

CCI



- Dose expansion phase

CCI



#### 12.1.4 Safety and Tolerability Endpoints

Safety and tolerability of MLN0128 will be assessed in each study phase based on the following:

- Incidence, duration, and severity of treatment-emergent AEs, including dose-limiting toxicity (see Section 8.2.1), SAEs, AEs resulting in dose modification or permanent discontinuation of study drug, and deaths within 30 days of the last dose of study drug;
- Changes in laboratory test results including chemistry and hematology;
- Changes in vital signs including blood pressure, pulse, and temperature;
- Changes in electrocardiogram results.

### 12.2 Analysis Populations

#### 12.2.1 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

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

For purposes of defining the MTD and/or expansion phase recommended dose(s) 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 at least 75% of the planned doses in Cycle 1 will be considered to have sufficient safety data/follow-up to support dose escalation. Subjects who withdraw from study before receiving 75% of the planned doses in the first cycle of treatment for reasons unrelated to study drug toxicity will be considered to have inadequate data to support dose escalation. 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.

#### **12.2.2 Efficacy Analysis**

The response-evaluable population will serve as the primary population for the analysis of tumor response and other efficacy-related data for the expansion cohorts. The response-evaluable population includes subjects who receive at least 1 dose of MLN0128 dose, have measurable disease at baseline, and undergo at least 1 post-baseline disease assessment.

### **12.3 Statistical Methods**

#### **12.3.1 Safety Analysis**

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

The observed DLT rate in each dose cohort and dose schedule will be calculated by the crude proportion of subjects who experience DLT during the first cycle of therapy. Multiple concurrent AEs 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 and schedule of MLN0128 and probability of DLT will be assessed by fitting various regression models such as  $E_{\max}$ , logistic and exponential model shapes.

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Adverse events will be coded using the latest available version of MedDRA. Treatment-emergent AEs are defined as AEs that start on or after the first dose of study drug and within 30 days of the last administration of study drug. 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 AE 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 and dose schedule 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. Adverse event incidence rates may also be calculated based on other measures of subject exposure (eg, total number of treatment cycles administered). All AEs will also be summarized by NCI-CTCAE version 4.0 severity grade and by relationship to each study drug. Additional summaries may also be provided for SAEs, and events resulting in the permanent discontinuation of 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.

#### **12.3.2 Efficacy Analysis**

The efficacy analyses for the expansion cohorts will be conducted based on the response-evaluable population in Section 12.2. The results of these analyses will be summarized for

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the renal cohorts. If there is a sufficient number of subjects, with a specific tumor type in the multi-tumor type cohort (ie, endometrial and bladder), then efficacy endpoints will also be summarized by tumor type.

#### Objective Response Rate

The objective response rate will be estimated for each tumor histology type evaluated 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 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 12-1](#) below. These conventions are based on the May 2007 FDA Guidance for Industry.<sup>(28)</sup>

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

**Table 12-1 Date of Progression or Censoring for Duration of Response**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
Non-protocol anticancer 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

The duration of stable disease will be evaluated for subjects with a best response of stable disease and will be defined as the number of days from the date of first dose to the date of progressive disease.

### Biomarkers

Descriptive statistics will be primarily used to summarize the biomarker data generated in this study. For continuous variables, the number of subjects with non-missing data, mean, either the standard error or standard deviation, median, 25<sup>th</sup> percentile (first quartile), 75<sup>th</sup> percentile (third quartile), minimum, and maximum will be presented. For discrete data, the frequency and percent distribution will be presented.

The effect of MLN0128 on the expression levels of selected biomarkers will be evaluated by calculating the difference in each biomarker from baseline, and the repeat post-baseline samples obtained during the course of the study. The Wilcoxon signed rank test will be used to identify any statistically significant ( $p < 0.05$ ) changes in biomarker levels. Additionally, the correlation among the various initial biomarker levels will be assessed by calculating Spearman's correlation coefficient between pairs of biomarkers.

Analysis of covariance (ANCOVA) models will be used to explore the relationship between the biomarker parameters and the estimated pharmacokinetic parameters. Nonparametric methods and/or nonlinear models may also be used to further examine the between biomarker and pharmacokinetic parameters.

## **12.4 Sample Size Determination**

### **12.4.1 Dose Escalation Phase**

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

### **12.4.2 Expansion Phase**

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

## **12.5 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 8.2.2. 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 toxicities from the current cohort during the site teleconferences before initiating enrollment into the next planned dose cohort.

### **12.6 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.

### 13. ETHICS

#### 13.1 Institutional Review Board or Ethics Committee

Prior to initiating the study, the Investigator will obtain written confirmation that the IRB or EC is properly constituted and compliant with all United States FDA requirements and local regulations. A copy of the confirmation from the IRB/EC will be provided to Millennium or its designee. The PI will provide the IRB/EC with all appropriate material, including the protocol, Investigator's Brochure, the ICF/PIC, 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/EC 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.

#### 13.2 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.

#### 13.3 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, Organic Law 15/1999 of 13 December 1999 on the DPA in Spain, 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/PIC and HIPAA authorization/DPA and provide the documents to Millennium or its designee for approval prior to submission to the IRB/EC.

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Millennium and the IRB/EC must approve the documents before they are implemented. If a subject is unable to sign the ICF/PIC and HIPAA authorization/DPA, a legal representative may sign for the subject. The investigator will provide copies of the signed ICF/PIC to each subject (or the subject's legal representative) and will maintain the original in the subject's record file.

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**14. 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.

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## 15. CASE REPORT FORMS AND SOURCE DOCUMENTS

Case report forms will be provided for each subject. The investigator must review and sign the completed CRFs to verify their accuracy.

CRFs must be filled out legibly and completed using a black ballpoint pen. Unless explicitly allowed in the CRF instructions, blank data fields are not acceptable. If a field is blank because the item was not done, the field will be marked “ND.” If the item is unknown, the field will be marked “UNK.” If the item is not applicable, the field will be marked “NA.” If the item is not available, the field will be marked “NAV.”

If an entry error has been made and the original CRF page is still at the study site, the error must be corrected on the CRF page by making a single straight line through the incorrect data and writing the correct data, allowing the original text to remain legible. Each correction must be initialed and dated by the person making the change. If corrections are made after review and signature by the Investigator, he or she must confirm and endorse the changes. ERRORS MAY NOT BE ERASED, AND WHITEOUT MAY NOT BE USED ON ANY STUDY- RELATED DOCUMENTS. The study staff will be queried for clarification regarding illegible or incomplete entries. There should be no writing in the margins.

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). The investigator must therefore agree to allow direct access to all source data. Subjects (or their legal representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If an investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an “interview” style of data verification.

A CRA designated by Millennium will compare the original CRFs with the original source documents at the study site and evaluate the CRFs for completeness and accuracy before returning them to Millennium or its designee for data management and analysis. If necessary, the study site personnel will be contacted for corrections and/or clarifications. Errors to CRFs that are identified after the original CRF page has been removed by the CRA will be corrected as described in the Study Reference Manual. The investigator or designee must also review and sign all Data Clarification Forms (DCF) or the corrections to the CRF

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to verify their accuracy prior to submission to Millennium or its designee. Data that are modified via DCFs must be supported in the source documents.

A copy of the CRF and any accompanying DCFs will be maintained in the investigator's file. Designated site personnel must complete CRFs as soon as possible after a subject visit, and the forms must be available for review at the next scheduled monitoring visit.

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## **16. 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.

**17. 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.

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**18. 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.

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**20. PROTOCOL ACCEPTANCE PAGE**

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

**Protocol Number:** INK128-001

**Investigational Product:** MLN0128 (also known as TAK-228 and INK128)

**Sponsor:** Millennium Pharmaceuticals, Inc.  
40 Landsdowne Street, Cambridge, MA USA 02139

**Medical Monitor:** Fabian Zohren, M.D.

**Date of Original Protocol:** November 3, 2009

**Date of Amendment 1:** December 3, 2009

**Date of Amendment 2:** January 28, 2010

**Date of Amendment 3:** March 31, 2010

**Date of Amendment 4:** July 20, 2010 (not implemented)

**Date of Amendment 5:** August 12, 2010

**Date of Amendment 6:** September 14, 2010

**Date of Amendment 7:** October 27, 2010

**Date of Amendment 8:** December 21, 2010

**Date of Amendment 9:** March 25, 2011

**Date of Amendment 10:** June 28, 2011

**Date of Amendment 11:** October 12, 2011

**Date of Amendment 12:** April 03, 2012

**Date of Amendment 13:** May 21, 2012

**Date of Amendment 14:** July 30, 2012

**Date of Amendment 15:** March 27, 2013

**Date of Amendment 16:** July 3, 2013

**Date of Amendment 17:** March 5, 2014

**Date of Amendment 18:** September 26, 2016

**Date of Amendment 19:** November 28, 2017

**Date of Amendment 20:** January 17, 2018

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

\_\_\_\_\_  
Investigator Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name of Investigator

Please return a copy of this form to Millennium Pharmaceuticals or its designee. Contact details will be provided to the investigator. Please retain a copy for your study files.

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**21. APPENDICES****21.1 ECOG Performance Status****Table 21-1 ECOG Performance Status**

<b>Grade</b>	<b>Description</b>
0	Normal activity. Fully active, able to carry on all predisease 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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.<sup>(29)</sup>

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**21.2 List of Relevant Cytochrome P450 Inhibitors and Inducers****Table 21-2 List of Relevant Cytochrome P450 Inhibitors and Inducers**

<b>Moderate CYP1A2 Inhibitors</b>		
methoxsalen	mexiletine	oral contraceptives
<b>Strong CYP1A2 Inhibitors</b>		
fluvoxamine	ciprofloxacin	enoxacin
zafirlukast		
<b>Clinically Relevant CYP Inducers (moderate* CYP1A2 and strong CYP3A4)</b>		
phenytoin	rifampin	ritonavir
teriflunomide	carbamazepine	enzalutamide
mitotane	phenytoin	St. John's wort

Source:

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2>

\* No strong CYP1A2 inducers could be identified in the above source at present

Note that these lists are not exhaustive. Please refer to the above link for further information and examples of other CYP inhibitors/inducers.

### 21.3 New York Heart Association Classification of Cardiac Disease

**Table 21-3 New York Heart Association Classification of Cardiac Disease**

<b>Class</b>	<b>Functional Capacity</b>	<b>Objective Assessment</b>
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.<sup>(30)</sup>

## 21.4 Amendment 20 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Amendment 20 are indicated. The corresponding text has been revised throughout the protocol.

**Change 1:** Specify cautionary use of CYP1A2 inhibitors and CYP1A2 and Cyp3A4 inducers as concomitant medications.

The primary change occurs in Section [8.9.9, Prior and Concomitant Medications](#).

Revised text: ~~Strong cytochrome CYP1A2 inhibitors, moderate CYP1A2 inducers, and strong and moderate CYP3A4 inducers should be administered with caution and at the discretion of the investigator.~~ **Moderate and strong cytochrome CYP1A2 inhibitors and moderate and strong CYP1A2 and CYP3A4 inducers should be administered with caution and at the discretion of the investigator.**

### Rationale for Change:

This change was made to address the use of moderate cytochrome CYP1A2 inhibitors and strong CYP1A2 inducers.

**Change 2:** [Remove dietary restrictions related to CYP inhibitors and inducers consistently within the protocol.](#)

The primary change occurs in the synopsis and exclusion criteria to align with Section [8.11, Dietary or Other Protocol Restrictions](#).

Deleted text: Subjects should not consume food or beverages containing the fruit or juice from grapefruits or Seville oranges within 7 days before first dose of study drug.

### Rationale for Change:

This change was made for consistency within the protocol with new data that remove the necessity for restrictions concerning CYP2C9 and 2C19.

**Change 3:** Update FDA guidance link.

The primary change occurs in the footnote to [Table 21-2](#).

Revised text: ~~fd a.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.~~  
**<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2>**

### Rationale for Change:

This change was made to provide the current FDA guidance.

**Change 4:** Add additional information to footnote.

The primary change occurs in the footnote to [Table 21-2](#).

Added **Please refer to the above link for further information and examples of**

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text: **other CYP inhibitors/inducers.**

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**Rationale for Change:**

This change was made to specify that additional information is available via the FDA guidance link.

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	17-Jan-2018 21:30 UTC

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