Title: A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies

NCT Number: NCT02412722

Protocol Approve Date: 27 November 2017

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

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CLINICAL STUDY PROTOCOL MLN0128-1004 AMENDMENT 3

MLN0128

A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies

Protocol Number:	MLN0128-1004
Indication:	Advanced nonhematologic malignancies
Phase:	1
Sponsor:	Millennium Pharmaceuticals, Inc.
Therapeutic Area:	Oncology

Protocol History

Original	30 September 2014
Amendment 1	25 March 2015
Amendment 2	14 May 2015
Amendment 3	27 November 2017

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Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

PPD	Signature	*Date DD Month YYYY*

Rationale for Amendment 3

This document describes the changes in reference to the protocol incorporating Amendment 3. The primary reason for this amendment is to update those sections affected by new nonclinical data for MLN0128 metabolism by specific cytochrome P450 (CYP) isoforms. The study's exclusion criteria, list of prohibited concomitant medications, list of relevant CYP inhibitors and inducers, and dietary restrictions related to CYP inhibitors and inducers have been updated accordingly. The required frequency of radiographic disease assessments for patients who have received at least 1 year of continuous MLN0128 treatment has also been reduced. Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix 14.7.

Changes in Amendment 3

1. Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.
2. Update the list of concomitant medications prohibited during the study.
3. Update the list of relevant CYP inhibitors and inducers.
4. Remove dietary restrictions related to CYP inhibitors and inducers.
5. Insert language to reduce the required frequency of radiographic disease assessments for patients who have received at least 1 year of continuous MLN0128 treatment per protocol.

PROTOCOL SUMMARY

Study Title: A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies

Number of Patients: Approximately 44 to 56 evaluable patients will be enrolled from 5 study centers in the United States.

Study Objectives

Primary

- To evaluate the safety and tolerability of MLN0128 milled active pharmaceutical ingredient (API) capsules administered both as a single agent and in combination with paclitaxel
- To characterize the effect of a high-fat meal on the pharmacokinetics (PK) of MLN0128 milled API capsules
- To characterize the PK of MLN0128 milled API capsules when administered on an empty stomach approximately 24 hours after paclitaxel infusion

Secondary

- To characterize the PK of MLN0128 milled API capsules versus unmilled API capsules, when administered on an empty stomach
- To evaluate the preliminary efficacy of MLN0128 milled API capsules when administered as a single agent and in combination with paclitaxel

Overview of Study Design:

This study is a multicenter, open-label, phase 1 trial of MLN0128 administered orally both as a single agent and in combination with intravenous (IV) infusions of paclitaxel in adult patients with advanced nonhematologic malignancies for whom standard, curative, or life-prolonging anticancer treatment does not exist or is no longer effective. The study will consist of 3 arms: a Single-Agent QD (daily dosing) Arm, a Combination Arm, and a Single-Agent QW (weekly dosing) Arm. The 3 arms will enroll in parallel and will administer study treatment in repeated 28-day cycles.

The Single-Agent QD Arm will test the safety, tolerability, and PK of MLN0128 milled API capsules when administered on an empty stomach and will additionally characterize the PK profile when taken with a standardized high-fat breakfast. In the same patients, the PK of MLN0128 unmilled API capsules when taken on an empty stomach will also be assessed as a point of reference for comparison of milled API capsule PK. The PK assessments will be performed during a PK Run-In period during which each patient will receive a total of three 4-mg doses of MLN0128 as described below:

- PK Run-In Visit 1: MLN0128 4-mg unmilled API capsule taken on an empty stomach.
- PK Run-In Visit 2 (24 hours [± 1 hr] after PK Visit 1): 24-hour postdose PK sample collected.
- PK Run-In Visit 3 (≥ 48 hours after PK Visit 1): MLN0128 4-mg milled API capsule taken with a standardized high-fat breakfast.
- PK Run-In Visit 4 (24 hours [± 1 hr] after PK Visit 3): 24-hour postdose PK sample collected.

- PK Run-In Visit 5 (≥ 48 hours after PK Visit 3): MLN0128 4-mg milled API capsule taken on an empty stomach.
- PK Run-In Visit 6 (24 hours [± 1 hr] after PK Visit 5): 24-hour postdose PK sample collected. Note: If scheduling permits, Visit 6 can be combined with Cycle 1 Day 1 of the Study Treatment period. That is, the 24-hour postdose PK sample for the Visit 5 PK dose can be drawn before the first administration of the patient's assigned Study Treatment dose if the timing allows.

Each patient in the Single-Agent QD Arm will complete the PK Run-In period within 14 days before Cycle 1 Day 1 of the Study Treatment period. Study treatment for the Single-Agent QD Arm will consist of repeated 28-day cycles of oral MLN0128 milled API capsules taken on an empty stomach. The first 6 patients enrolled into the Single-Agent QD Arm Study Treatment period will receive MLN0128 at 4 mg once daily (QD). An evaluation of safety and tolerability will be conducted after these first 6 patients have completed Cycle 1 to determine the dose to be administered during the Study Treatment period for the next patients enrolled into the Single-Agent QD Arm. Safety evaluations will continue before enrolling each subsequent cohort into the Single-Agent QD Arm. A total of 16 subjects will complete the protocol-specified PK evaluations in the Single-Agent QD Arm.

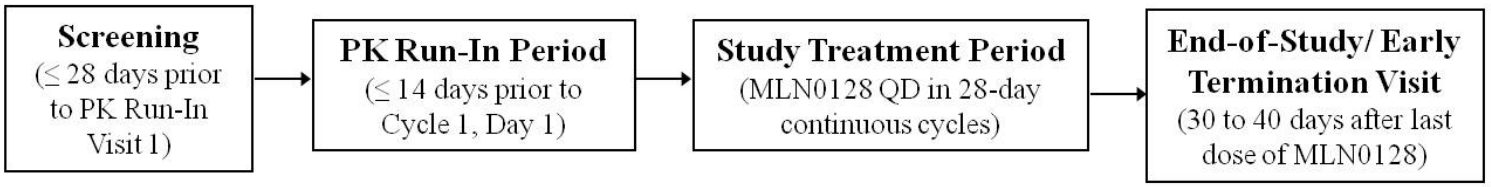
The Combination Arm will test the safety, tolerability, and PK of MLN0128 milled API capsules when administered on an empty stomach in combination with paclitaxel. Paclitaxel (80 mg/m^2) will be administered as an IV infusion on Days 1, 8 (± 1 day), and 15 (± 1 day) of each 28-day cycle according to the institution's standard clinical practice. MLN0128 will be administered QD × 3 days each week (QW) of each cycle, beginning 24 hours after completion of the Day 1 paclitaxel infusion; ie, MLN0128 will be administered on an empty stomach on Days 2 through 4, 9 through 11, 16 through 18, and 23 through 25 of every 28-day cycle. The starting MLN0128 dose for the Combination Arm will be 6 mg (QD × 3 days QW). Plasma samples to characterize the PK of MLN0128 will be collected on Cycle 1 Day 2. Consistent with the Single-Agent QD Arm, an interim safety and tolerability review will be conducted for the Combination Arm after the initial cohort of 6 patients has completed Cycle 1. According to standard dose escalation rules on the basis of the safety and tolerability observed in the initial 6 evaluable patients, the dose of MLN0128 (QD × 3 days QW) for the next cohort of 6 patients will be either reduced, maintained, or escalated.

The Single-Agent QW Arm will evaluate the safety, tolerability, and PK of MLN0128 milled API when administered on an empty stomach in 2 sequential cohorts, each consisting of 6 to 12 patients. Initially, 6 patients in Cohort 1 will receive 20 mg of MLN0128 capsules based on milled API once every week (QW). Serial plasma specimens will be collected for evaluation of MLN0128 PK. A safety and tolerability assessment will be performed after the last patient in the cohort completes Cycle 1. If ≥2 patients experience a dose-limiting toxicity (DLT) during Cycle 1, then the starting dose of MLN0128 milled API for the subsequent cohort (Cohort 2) will be reduced to 15 mg QW. If ≤1 patient in Cohort 1 experiences a DLT in Cycle 1, then the dose of milled MLN0128 in Cohort 2 will be increased to 30 mg QW. If the dose of MLN0128 milled API is deemed safe in any cohort based on 3+3 rules, then the cohort may be expanded to 12 patients to confirm the recommended phase 2 dose for single-agent MLN0128 milled API capsules when administered QW. Plasma samples to characterize the PK of MLN0128 will be collected on Cycle 1 Day 1.

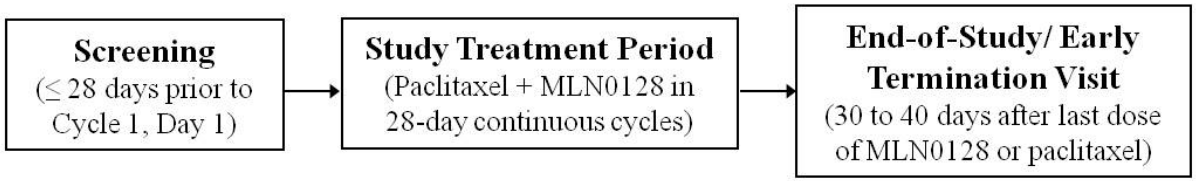
Study Population: To be eligible for the study, a patient must be ≥ 18 years of age before the Screening visit; have advanced nonhematologic malignancies, with the exception, of primary brain tumor; and have failed or be ineligible for standard-of-care therapy. Patients with a history of treated brain metastasis may be eligible provided, that they are off treatment, have no sign of disease progression or hemorrhage, and have no ongoing requirement for dexamethasone or anti-epileptic drugs. All patients must have an Eastern Cooperative Oncology Group Performance Status of ≤ 1, adequate clinical laboratory values, and acceptable left ventricular ejection fraction.
Duration of Study: In the absence of unacceptable treatment-related toxicity or disease progression, patients may receive study 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 if, in the opinion of the investigator, the patient is benefitting from treatment.

STUDY FLOW DIAGRAM

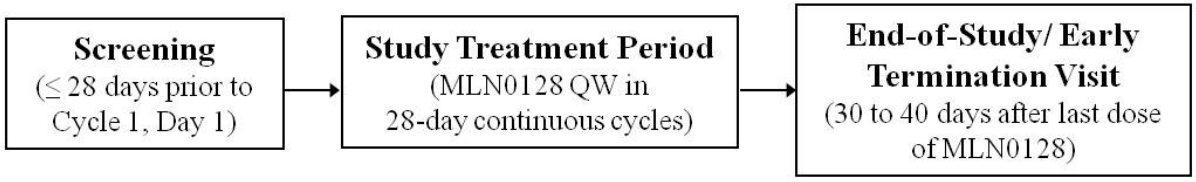
Single-Agent QD Arm



Combination Arm



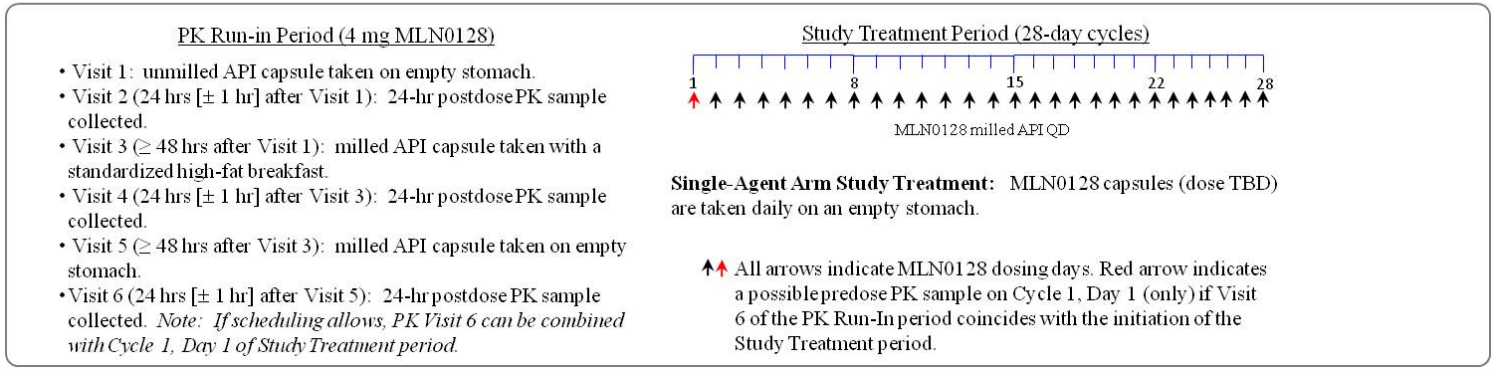
Single-Agent QW Arm



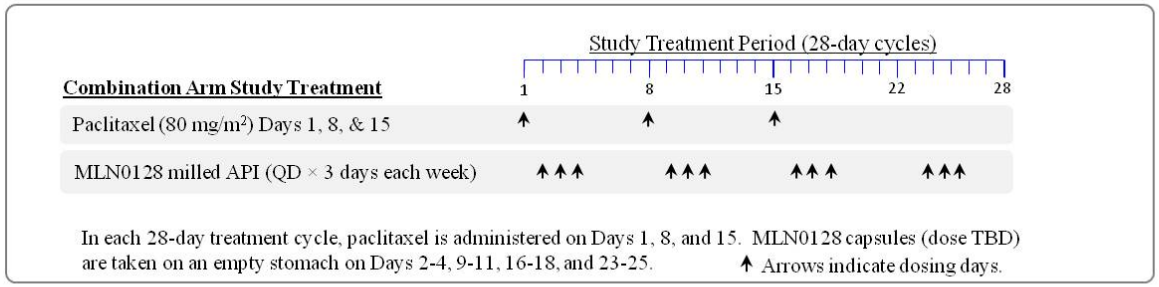
Abbreviations: PK = pharmacokinetic; QD = once daily; QW = once weekly.

STUDY DRUG DOSING DIAGRAM

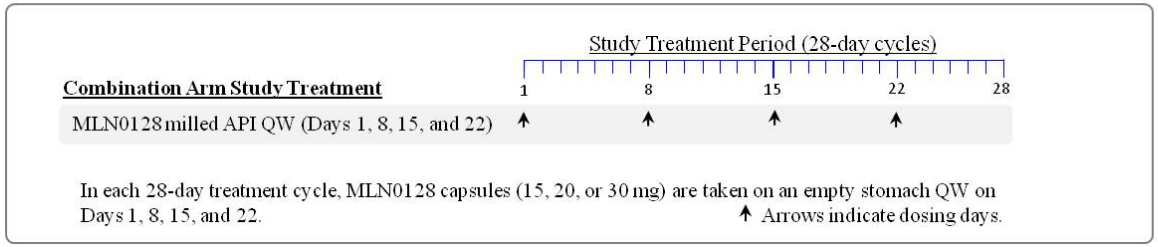
Single-Agent QD Arm



Combination Arm



Single-Agent QW Arm



Abbreviations: API = active pharmaceutical ingredient; hr(s)= hour(s); PK = pharmacokinetic; QD = once daily; QW = once weekly; TBD = to be determined.

SINGLE-AGENT QD AND SINGLE-AGENT QW ARMS SCHEDULES OF EVENTS

Table 1-1 Single-Agent QD and Single-Agent QW Arms Schedule of Events

		PK Run-In Period (≤ 14 Days of Cycle 1 Day 1) Single-Agent QD Arm Only						Study Treatment Period (28-Day Cycles)								
								Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	EOS/ ET Visit[f]
	Screening[a]	Visit 1	Visit 2[b]	Visit 3[c]	Visit 4[b]	Visit 5[d]	Visit 6[b]	Day 1	Day 2[e]	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
Study Procedures																
Informed consent	X															
Eligibility criteria	X															
Demographics	X															
Medical history	X															
Height	X															
Weight	X	X				X		X			X	X		X	X	X
Physical examination	X	X		X		X		X			X	X		X	X	X
Vital signs[g]	X	X		X		X		X		X	X	X	X	X	X	X
ECOG performance status	X							X			X	X		X	X	X
ECHO/MUGA	X															
Single, 12-lead ECG[h]	X1	X2[h]		X2[h]		X2[h]		X2[h]								X1
Disease assessment[i]	X											Q2C			Q2C	X
Concomitant medications and procedures reporting	X	Recorded from first dose of study drug through 30 days after the last dose of study drug														
SAE reporting[j]	**SAEs**[j] recorded from signing of the informed consent form through 30 days after the last study drug dose															
Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug														

Table 1-1 Single-Agent QD and Single-Agent QW Arms Schedule of Events

	Screening[a]	PK Run-In Period (≤ 14 Days of Cycle 1 Day 1) Single-Agent QD Arm Only						Study Treatment Period (28-Day Cycles)								EOS/ ET Visit[f]
								Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	
		Visit 1	Visit 2[b]	Visit 3[c]	Visit 4[b]	Visit 5[d]	Visit 6[b]	Day 1	Day 2[e]	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
MLN0128 Dosing																
Single-Agent QD Arm		X		X		X		QD continuously (cohort-specific dose TBD)								
Single-Agent QW Arm								Days 1, 8, 15, 22, and 28 of each 28-day cycle (see Section 4.1)								
Samples and Laboratory Assessments																
Hematology	X1	X1		X1		X1		X1[k]		X1	X1	X1[j]	X1	X1	X1[j]	X1
Chemistry	X1	X1		X1		X1		X1[k]		X1	X1	X1[j]	X1	X1	X1[j]	X1
Urinalysis	X1[l]	X1				X1		X1[k]			X1	X1[j]		X1	X1[j]	X1
Pregnancy test[m]	X1	X1[m]						X1[m]								
Coagulation (PT/INR, aPTT)	X1	X1						X1			X1	X1		X1	X1	X1
Fasting serum glucose[n]	X1	X1						X1		X1	X1	X1			X1	X1
In-home fasting glucose monitoring[o]								Measured daily (predose), See Section 7.4.16								
Fasting lipid profile	X1[p]							X1				X1			X1	X1
HbA1c	X1							X[q]				X[q]			Q3C[q]	
CCI																
Blood sample for PK analysis for Single-Agent QD Arm (see Table 1-2)[s]		X8	X1	X8	X1	X8	X1									
Blood sample for PK analysis for Single-Agent QW Arm (see Table 1-3)[s]								X8[t]	X1[t]							

Table 1-1 Single-Agent QD and Single-Agent QW Arms Schedule of Events

		PK Run-In Period (≤ 14 Days of Cycle 1 Day 1) Single-Agent QD Arm Only						Study Treatment Period (28-Day Cycles)								EOS/ ET Visit[f]
								Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	
	Screening[a]	Visit 1	Visit 2[b]	Visit 3[c]	Visit 4[b]	Visit 5[d]	Visit 6[b]	Day 1	Day 2[e]	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
Abbreviations: aPTT = activated partial thromboplastin time; C = cycle; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end-of-study; ET = early termination; HbA1c = glycosylated hemoglobin; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic; PT = prothrombin time; Q = every; SAE = serious adverse event; TBD = to be determined; X# = number of samples required (eg, 2 samples = X2).															
Tests and procedures should be performed on schedule, but occasional changes are allowable (± 2 days) with permission from the medical monitor for holidays, vacations, and other administrative reasons.																
a Screening assessments are performed within 28 days before PK Visit 1. Screening assessments performed not more than 3 days before the PK Visit 1 dose need not be repeated, unless otherwise specified.																
b Visit should occur 24 hours after the prior PK Run-In Visit.																
c PK Run-In Visit 3 should occur at least 48 hours after PK Run-In Visit 1.																
d PK Run-In Visit 5 should occur at least 48 hours after PK Run-In Visit 3.																
e The Day 2 visit occurs only on Cycle 1 for patients in the Single-Agent QW Arm to collect a blood sample for PK analysis.																
f Patients will attend an EOS/ET visit 30 to 40 days after receiving their last dose of study drug.																
g Vital sign measurements include blood pressure (diastolic and systolic), heart rate, and temperature.																
h When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first. On Cycle 1 Day 1 and Cycle 2 Day 1, an ECG should be completed predose in addition to 2 hours (± 30 min) postdose.																
i Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be obtained within 4 weeks before the first dose of MLN0128. . The same imaging modality (CT [with contrast], MRI, or bone scan) should be used on a patient throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. Scans are permitted up to 7 days in advance of the scheduled visit. At EOS, tumor assessments will be done only on patients who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks. See Section 7.4.18. For long term patients, defined as study participation (≥1 year, a CT (with contrast)/MRI of chest, abdomen, and pelvis will be obtained at intervals of up to every 4 cycles (plus or minus 7 days) as clinically indicated.																
j Including serious pretreatment events; see Section 9.1.1.																
k May be assessed up to 24 hours before the study visit.																
l For screening, creatinine clearance must be ≥ 50 mL/min based either on Cockroft-Gault estimate or based on a 12- or 24-hour urine collection.																
m In the Single-Agent QD Arm, a serum pregnancy test will be performed only for patients of childbearing potential during screening and again at PK Run-In Visit																

Table 1-1 Single-Agent QD and Single-Agent QW Arms Schedule of Events

		PK Run-In Period (≤ 14 Days of Cycle 1 Day 1) Single-Agent QD Arm Only						Study Treatment Period (28-Day Cycles)								
								Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	
	Screening[a]	Visit 1	Visit 2[b]	Visit 3[c]	Visit 4[b]	Visit 5[d]	Visit 6[b]	Day 1	Day 2[e]	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	EOS/ ET Visit[f]

1 (baseline) if the screening test was performed > 3 days before PK Run-In Visit 1 (a urine test may be performed at PK Visit 1 if the serum results are not yet available). In the Single-Agent QW Arm, a serum pregnancy test will be performed only for patients of childbearing potential during screening and again at Cycle 1 Day 1 (baseline) if the screening test was performed > 3 days before the first dose of any study drug (a urine test may be performed at Cycle 1 Day 1 if the serum results are not yet available). The results must be negative within 3 days before PK Visit 1 in the Single-Agent QD Arm or within 3 days before Cycle 1 Day 1 in the Single-Agent QW Arm, or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, at the request of an independent ethics committee/institutional review board, or if required by local regulations.

n Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for ≥ 8 hours before the assessment) for each measurement. See Section 7.4.15.

o Patients will be given a glucometer on Cycle 1 Day 1 to monitor daily fasting glucose levels at home throughout Cycles 1 and 2, and will be instructed to notify the study clinician when the fasting glucose is abnormal (ie, ≥ 150 mg/dL). In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic. See Section 7.4.16 for further instruction.

p To be completed within 14 days of PK Visit 1 dosing.

q During the Study Treatment period, HbA1c will be tested on Day 1 of Cycles 2 through 5, and on Day 1 of every third cycle thereafter (ie, Cycle 8, 11, 14, etc).

r To be collected predose on PK Run-In Visit 1 in the Single-Agent QD arm and predose on Cycle 1 Day 1 in the Single-Agent QW Arm.

s Blood samples for PK analysis will be performed according to the schedule presented in Table 1-2 for patients in the Single-Agent QD Arm and in Table 1-3 for patients in the Single-Agent QW Arm.

t The blood samples for PK analysis in the Single-Agent QW Arm will be performed on Cycle 1 only (see Table 1-3).

Table 1-2 Pharmacokinetic Sampling Time Points for the Single-Agent QD Arm

	PK Run-In Period (≤ 14 Days Before Cycle 1 Day 1 of Study Treatment Period)					
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
MLN0128 Dosing:	4 mg (**unmilled** API) taken on an empty stomach[a]		4 mg (**milled** API) taken after a high-fat breakfast[b]		4 mg (**milled** API) taken on an empty stomach[a]	
PK Sampling Time Points						
Predose (within 0.5 hours)	X1[a]		X1[b]		X1[a]	
0.5 hours postdose (± 10 min)	X1		X1		X1	
1 hour postdose (± 10 min)	X1		X1		X1	
2 hours postdose (± 30 min)	X1		X1		X1	
3 hours postdose (± 30 min)	X1		X1		X1	
4 hours postdose (± 30 min)	X1		X1		X1	
6 hours postdose (± 30 min)	X1		X1		X1	
8 hours postdose (± 45 min)	X1		X1		X1	
24 hours postdose (± 1 hr)		X1		X1		X1[c]

Abbreviations: API = active pharmaceutical ingredient; min = minutes; PK = pharmacokinetic; X# = number of samples required (eg, 1 sample = X1).

a Patients will be instructed to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours). Patients will then receive study drug with a full glass of water (250 mL).

b Patients will report to the site fasted, having had nothing to eat or drink for at least 8 hours before the scheduled time of the high-fat breakfast. Patients will then be given a standardized, high-fat breakfast that they are required to finish within 30 minutes (+5 min). Patients will immediately receive study drug with a full glass of water (250 mL) within 5 minutes of the completion of the meal.

c If scheduling permits, Visit 6 can coincide with Cycle 1 Day 1 of the Study Treatment period. That is, the 24-hour PK sample following administration of the Visit 5 PK Run-In dose can be drawn before the first administration of the patient's assigned Study Treatment dose if the timing allows.

Table 1-3 Pharmacokinetic Sampling Time Points for the Single-Agent QW Arm

PK Sampling Time Point	Cycle 1 Day 1	Cycle 1 Day 2
Predose (within 0.5 hours)	X1[a]	
0.5 hours postdose (± 10 min)	X1	
1 hour postdose (± 10 min)	X1	
2 hours postdose (± 30 min)	X1	
3 hours postdose (± 30 min)	X1	
4 hours postdose (± 30 min)	X1	
6 hours postdose (± 30 min)	X1	
8 hours postdose (± 45 min)	X1	
24 hours postdose (± 1 hour)		X1

Abbreviations: min = minutes; PK = pharmacokinetic; X# = number of samples required (eg, 1 sample = X1).

a Patients will hold their medication in the morning and take their MLN0128 dose after the predose PK sample has been collected.

COMBINATION ARM SCHEDULES OF EVENTS

Table 1-4 Combination Arm Schedule of Events

	Screening[a]	Study Treatment Period (28-Day Cycles)								EOS/ ET Visit[b]
		Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	
		Day 1	Day 2	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
Study Procedures										
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Height	X									
Weight	X	X			X	X		X	X	X
Physical examination	X	X			X	X		X	X	X
Vital signs[c]	X	X		X	X	X	X	X	X	X
ECOG performance status	X	X			X	X		X	X	X
ECHO/MUGA	X									
Single, 12-lead ECG[d]	X1	X2[d]								X1
Disease assessment[e]	X					Q2C[e]			Q2C[e]	X[e]
Concomitant medications & procedures reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug								
SAE reporting[f]	**SAEs**[f] recorded from signing of the informed consent form through 30 days after the last dose of study drug									
Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug								
Paclitaxel administration		X		X	X	X	X	X	X[g]	
MLN0128 administration			Days 2-4, 9-11, 16-18, and 23-25 of each 28-day cycle							

Table 1-4 Combination Arm Schedule of Events

	Screening[a]	Study Treatment Period (28-Day Cycles)								EOS/ ET Visit[b]
		Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	
		Day 1	Day 2	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
Samples/Laboratory Assessments										
Hematology[h]	X1	X1[i]		X1	X1	X1[i]	X1	X1	X1[i]	X1
Chemistry[h]	X1	X1[i]		X1	X1	X1[i]	X1	X1	X1[i]	X1
Urinalysis	X1[j]	X1[i]			X1	X1[i]		X1	X1[i]	X1
Pregnancy test[k]	X1	X1[k]								
Coagulation (PT/INR, aPTT)	X1	X1			X1	X1		X1	X1	X1
Fasting serum glucose[l]	X1	X1		X1	X1	X1			X1	X1
In-home daily fasting glucose monitoring[m]			Measured daily (predose), See Section 7.4.16							
Fasting lipid profile	X1[n]	X1				X1			X1	X1
HbA1c[o]	X1	X[o]				X[o]			Q3C[o]	
CCI										
Blood sample for PK analysis (Cycle 1, only; see Table 1-5)[q]			X8							

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle; CT = computed axial tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end-of-study; ET = early termination; HbA1c = glycosylated hemoglobin; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic; PT = prothrombin time; Q = every; SAE = serious adverse event; X# = the number of samples required (eg, 2 samples = X2).

Tests and procedures should be performed on schedule, but occasional changes are allowable (± 2 days) with permission from the medical monitor for holidays, vacations, and other administrative reasons.

a Screening assessments are performed within 28 days before the Cycle 1 Day 1 dose. Screening assessments performed ≤ 3 days before the first dose will qualify as baseline assessments and need not be repeated, unless otherwise specified.

b Patients will attend an EOS/ET visit 30 to 40 days after receiving their last dose of study drug.

Table 1-4 Combination Arm Schedule of Events

		Study Treatment Period (28-Day Cycles)								
		Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	EOS/ ET Visit[b]
	Screening[a]	Day 1	Day 2	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	

c Vital sign measurements include blood pressure (diastolic and systolic), heart rate, and temperature.

d When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first. On Cycle 1 Day 1 and Cycle 2 Day 1, an ECG should be completed predose in addition to 2 hours (± 30 min) postdose.

e Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be obtained within 4 weeks before the first dose of MLN0128 and at Cycle 3 Day 1, after which CT (with contrast) or MRI may be performed every 2 cycles (ie, Cycle 5 Day 1, Cycle 7 Day 1, Cycle 9 Day 1, etc), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] MRI, or bone scan) should be used on a patient throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. Scans are permitted up to 7 days in advance of the scheduled visit. At EOS, tumor assessments will be done only on patients who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks. See Section 7.4.18 for more details.

f Including serious pretreatment events; see Section 9.1.1.

g Paclitaxel may be administered on Cycle 7 and beyond at the discretion of the investigator.

h Full hematology and chemistry panels are to be tested and reviewed by the investigator or appropriate designee before administering paclitaxel on Day 1 of each treatment cycle through Cycle 6.

i May be assessed up to 24 hours before the study visit.

j For screening, creatinine clearance must be ≥ 50 mL/min based either on Cockroft-Gault estimate or based on a 12- or 24-hour urine collection.

k A serum pregnancy test will be performed only for patients of childbearing potential during screening and again at Cycle 1 Day 1 (baseline) if the screening test was performed > 3 days before the first dose of any study drug (a urine test may be performed at Cycle 1 Day 1 if the serum results are not yet available). The results must be negative within 3 days before Cycle 1 Day 1, or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, at the request of an independent ethics committee/institutional review board, or if required by local regulations.

l Fasting serum glucose will be measured in the clinic before study drug dosing (and prior to administration of any prophylactics for paclitaxel). Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic. See Section 7.4.15.

m Patients in the Combination Arm will be given a glucometer on Cycle 1 Day 1 to monitor daily fasting glucose levels at home throughout Cycles 1 and 2, and will be instructed to notify the study clinician when the fasting glucose is abnormal (ie, ≥ 150 mg/dL). See Section 7.4.16 for further instruction.

n To be completed within 14 days of Cycle 1 Day 1 dosing.

o During the Study Treatment period, HbA1c will be tested on Day 1 of Cycles 2 through 5 and on Day 1 of every third cycle thereafter (ie, Cycle 8, 11, 14, etc).

p To be collected predose on Cycle 1 only.

Table 1-4 Combination Arm Schedule of Events

		Study Treatment Period (28-Day Cycles)								
		Cycles 1 and 2				Cycles 3, 4, 5, and 6			Cycle ≥ 7	
	Screening[a]	Day 1	Day 2	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	EOS/ ET Visit[b]
q In Cycle 1 only, blood samples for PK analysis will be performed according to the schedule presented in Table 1-5.										

Table 1-5 Pharmacokinetic Sampling Time Points for the Combination Arm

PK Sampling Time Point	Cycle 1 Day 2
Predose (within 0.5 hours)	X1[a]
0.5 hours postdose (± 10 min)	X1
1 hour postdose (± 10 min)	X1
2 hours postdose (± 30 min)	X1
3 hours postdose (± 30 min)	X1
4 hours postdose (± 30 min)	X1
6 hours postdose (± 30 min)	X1
8 hours postdose (± 45 min)	X1

Abbreviations: min = minutes; PK = pharmacokinetic; X# = number of samples required (eg, 1 sample = X1).

a Patients will hold their medication in the morning and take their MLN0128 dose after the predose PK sample has been collected.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
4E-BP1	eukaryotic initiation factor 4-binding protein
AE	adverse event
AKT	serine/threonine-specific protein kinase (also known as protein kinase B)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-inf}}$	area under the plasma concentration versus time curve from zero extrapolated to infinity
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from zero to the last measurable concentration
CI	confidence interval
C_{max}	maximum (peak) concentration
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ER+	estrogen receptor positive
FBG	fasting blood glucose
GCP	Good Clinical Practice
HbA1c	glycosylated hemoglobin
HDPE	high-density polyethylene
HER2−	human epidermal growth factor receptor-2 negative
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee

Abbreviation	Term
IRB	institutional review board
IV	intravenous(ly)
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian (or mechanistic) target of rapamycin
MUGA	multiple gated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PI3K	phosphoinositide 3-kinase
PI3Kα	phosphoinositide 3-kinase alpha isoform
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PT/INR	prothrombin time/international normalized ratio
QD	*quaque die*; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
S473	Serine 473
SAE	serious adverse event
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse events
T_{max}	first time of occurrence of maximum (peak) concentration
TORC1	mammalian (or mechanistic) target of rapamycin complex 1
TORC2	mammalian (or mechanistic) target of rapamycin complex 2
ULN	upper limit of the normal range
US	United States
USPI	United States Prescribing Information
WBC	white blood cell

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

The mammalian (or mechanistic) target of rapamycin (mTOR) is a central regulator of cell growth, metabolism, and angiogenesis that functions in 2 distinct multiprotein complexes: mTOR complex 1 (TORC1) and mTOR complex 2 (TORC2). Like rapamycin, several newly approved rapalogs (temsirolimus and everolimus) are specific and allosteric inhibitors of TORC1 but only partially inhibit TORC1 substrates. They do not directly inhibit TORC2, which has shown to be an emerging target in cancer research. MLN0128 (formerly INK128) is a novel, selective, orally bioavailable mTOR inhibitor that targets both TORC1 and TORC2, which may lead to increased antitumor activity.

1.1.2 Study Drug

MLN0128 is being developed for the non-oncology indication of bronchiolitis obliterans syndrome, an inflammatory disease in the lung.

In oncology, MLN0128 is being investigated as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or antihormonal agents. MLN0128 is also being developed in combination with MLN1117 (an oral phosphoinositide-3-kinase [PI3K] alpha isoform [PI3Kα] inhibitor) as a treatment for advanced nonhematologic malignancies.

1.2 Nonclinical Experience

MLN0128 is an orally available, potent, and highly selective adenosine triphosphate competitive inhibitor of mTOR kinase that exhibits dual specificity against both the TORC1 and TORC2 complexes.

In vitro studies have demonstrated that MLN0128 selectively and potently inhibits mTOR kinase (1 nM). Relative to mTOR inhibition, MLN0128 has > 100-fold less potency on class I (PI3K isoforms α, β, γ, and δ), class II (PI3KC2α and PI3K2Cβ), and class III (VPS34) PI3K family members. MLN0128 inhibits (> 80%) the biochemical activity of 5 kinases (mTOR, DNA-PK, PDGFRα, Flt3, and CK1 epsilon kinases) out of a panel of 222 protein kinases. Out of a panel of 402 distinct kinases, MLN0128 inhibits the ligand binding of only 10 receptor and intracellular protein kinases (ACVR1, BMPR1B, CSF1R,

CSNK1D, CSNK1E, DDR1, MEK1, MEK2, PDGFRα, and RIPK2). MLN0128 also displays potent cellular inhibition of both the TORC1 and TORC2 pathway with cellular pharmacodynamically active concentrations at 50% inhibition values of < 10 nM.

MLN0128, administered orally in multiple human tumor xenograft mouse models, can inhibit angiogenesis and tumor growth by inhibiting mTOR signaling at plasma concentrations associated with in vitro inhibition of mTOR in a dose- and time-dependent manner. These effects display a clear pharmacokinetic (PK)-to-pharmacodynamic relationship.[(1)] MLN0128 inhibits both the phosphorylation of S6 and eukaryotic initiation factor 4-binding protein (4E-BP1), the downstream substrates of TORC1, and selectively inhibits serine/threonine-specific protein kinase (AKT) phosphorylation at Serine 473 (S473), as evidenced by decreased pAKT, the downstream substrate of TORC2.[(1, 2, 3)] Dual TORC1/2 inhibition mitigates the feedback activation of AKT, which is known to cause resistance to TORC1-only inhibitors such as rapamycin.[(4)] MLN0128 inhibits mTOR signaling and has demonstrated anticancer activity against a number of human solid tumor cell-line xenograft mouse models, including phosphatase and tensin homolog mutant endometrial, breast, and renal cell carcinomas.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN0128 may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

The MLN0128 clinical development program is designed to investigate the safety, PK, pharmacodynamics, and preliminary efficacy of MLN0128 for the treatment of advanced solid tumors and hematologic malignancies, either as a single agent or in combination with chemotherapy and/or human epidermal growth factor receptor-2 negative (HER2-)-targeting agents. Single-agent MLN0128 is in clinical development with phase 1 studies in patients with advanced nonhematological malignancies (INK128-001) and in patients with relapsed or refractory multiple myeloma or Waldenström's macroglobulinemia (INK128-002; completed). A third phase 1 study of MLN0128 is ongoing in combination with paclitaxel with or without trastuzumab in patients with advanced solid tumors (INK128-003). Also, a phase 1b/2 study is ongoing to evaluate MLN0128 in combination with either exemestane or fulvestrant in postmenopausal women with estrogen receptor-positive (ER+)/HER– advanced or metastatic breast cancer who have disease progression after previous treatment with everolimus (Study C31001). Additionally, the combination of MLN0128 plus MLN1117 (an oral PI3Kα inhibitor) is being evaluated in a phase 1b study in adult patients

with advanced nonhematologic malignancies (Study C32001). Further details on these studies are provided in the MLN0128 IB.

Clinical Pharmacokinetics of MLN0128

The PK parameters measured for MLN0128 in the phase 1 clinical studies have been generally consistent across a range of doses and schedules. MLN0128 has shown linear PK and fast oral absorption with single-dose first time of occurrence of maximum (peak) concentration (T_{max}) occurring between 1 and 4 hours after dosing. The mean terminal disposition half-life ($t_{1/2}$) of MLN0128 is approximately 8 hours, and no accumulation has been observed in plasma after repeat daily dosing. The PK properties of MLN0128 are further detailed in the IB.

1.4 Study Rationale

The sponsor has developed MLN0128 capsules based on milled active pharmaceutical ingredient (API). This phase 1 study will determine the safety, tolerability, and PK of these capsules administered as a single agent and in combination with paclitaxel. The PK of the MLN0128 milled API capsules will also be characterized when administered with a standardized high-fat breakfast.

The safety and tolerability observed in this study will inform the selection of the recommended phase 2 doses (RP2Ds) for MLN0128 milled API capsules when administered on 3 dosing schedules (single-agent once-daily [QD], single-agent once-weekly [QW] and QD × 3 days QW in combination with paclitaxel), that will be further investigated in the clinical development of MLN0128.

The study will consist of 3 arms: the Single-Agent QD Arm, the Combination Arm, and the Single-Agent QW Arm. During the Study Treatment period, patients in all 3 treatment arms will receive MLN0128 milled API capsules at prespecified doses, taken on an empty stomach.

Patients enrolled in the Single-Agent QD Arm will also participate in a PK Run-In period before entering the Study Treatment period. The PK Run-In period will determine the PK of MLN0128 milled API capsules when administered on an empty stomach and also after a standardized meal. In these same patients, the PK of MLN0128 unmilled API capsules when taken on an empty stomach will also be determined. The MLN0128 dose selected for the PK Run-In period (4 mg) is lower than the current maximum tolerated dose (MTD) of 6 mg MLN0128 when administered on a QD schedule. The 4 mg dose of MLN0128 is

considered a safe starting dose to evaluate the single-dose PK characteristics during the PK Run-In period, followed by evaluation of safety and tolerability of single-agent QD dosing during the Study Treatment period. MLN0128 Study Treatment doses for subsequent cohorts may either be escalated or de-escalated, depending upon tolerability observed in the prior cohort.

The Combination Treatment Arm will investigate MLN0128 in combination with paclitaxel. The proposed dosing regimens for the Combination Treatment Arm are based on an understanding of the proposed mechanism of action of MLN0128 as an mTORC1/mTORC2 inhibitor and a desire to avoid interference with paclitaxel. MLN0128 has been shown to induce G1 cell-cycle arrest. Paclitaxel is known to block the progression of cells through G2 into mitosis, and this G2-M arrest has been proposed to be a prerequisite step for apoptosis induced by paclitaxel.[(5)] Pretreatment of mTOR inhibitors will arrest cells in the G1 phase and antagonize the toxic effect of paclitaxel.[(6)] Accordingly, MLN0128 will be given 24 hours after paclitaxel administration so as not to interfere with the mechanism of paclitaxel. Nonclinical in vivo xenograft data also suggest that administration of MLN0128 approximately 24 hours following paclitaxel infusion may provide more synergy in tumor cell kill. In addition, both rapamycin and MLN0128 significantly enhanced paclitaxel-induced apoptosis when given 12 to 24 hours after chemotherapy administration (INK128-003 data).[(7)]

The Single-Agent QW Arm will evaluate the safety, tolerability and PK of milled MLN0128 API capsules using a QW dosing schedule. On the basis of biopharmaceutical considerations of API solubility in relation to the dose of MLN0128, the change from unmilled to milled API may result in faster absorption, and possibly result in a higher maximum observed plasma concentration (C_{max}) than that observed with unmilled API, which could potentially alter the safety profile of MLN0128. The safety and tolerability observed in this treatment arm will inform the selection of the RP2Ds for MLN0128 milled API capsules when administered QW and will be further investigated in the clinical development of MLN0128.

The current MTD of MLN0128 unmilled API capsules when administered 24 hours after completion of a paclitaxel infusion (80 mg/m^2 intravenously [IV] on Days 1, 8, and 15) in a 28-day cycle is 10 mg when administered QD × 3 days QW, and the RP2D regimen is 8 mg QD × 3 days QW. The starting dose of MLN0128 6 mg milled API capsules administered QD × 3 days QW beginning 24 hours after completion of a paclitaxel infusion is considered

a safe starting dose. Depending on tolerability, MLN0128 dose regimens for subsequent cohorts in the Combination Arm may either be escalated or de-escalated.

CCI

1.5 Potential Risks and Benefits

The most common treatment-emergent adverse events (TEAEs) observed with single-agent MLN0128 unmilled API capsules are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual mTORC1/2 inhibitors. Treatment-emergent adverse events observed across MLN0128 single-agent studies with unmilled API capsules include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, and increased blood creatinine. In general, observed toxicities have been mostly Grade 1 or Grade 2 and have been manageable with supportive care and/or an MLN0128 dose interruption or reduction.

During this study, risk mitigation strategies include, but are not limited to, strict application of the study eligibility criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, guidelines for dose modification, and regular monitoring of adverse events (AEs) and serious adverse events (SAEs) by the sponsor.

The benefits of MLN0128 are discussed in Section 1.1.2. Further details are presented in the MLN0128 IB.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are:

- To evaluate the safety and tolerability of MLN0128 milled API capsules administered both as a single agent and in combination with paclitaxel
- To characterize the effect of a high-fat meal on the PK of MLN0128 milled API capsules
- To characterize the PK of MLN0128 milled API capsules when administered on an empty stomach approximately 24 hours after paclitaxel infusion

2.2 Secondary Objective

The secondary objectives are:

- To characterize the PK of MLN0128 milled API capsules versus unmilled API capsules, when administered on an empty stomach
- To evaluate the preliminary efficacy of MLN0128 milled API capsules when administered as a single agent and in combination with paclitaxel

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints are:

- TEAEs, SAEs
- Ratio of geometric means and associated 90% confidence intervals (CIs) of the maximum (peak) concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from zero to the last measurable concentration ($AUC_{0\text{-last}}$), and AUC from zero extrapolated to infinity ($AUC_{0\text{-inf}}$) of a single dose of MLN0128 milled API capsules administered following a high-fat breakfast versus when administered on an empty stomach

- PK parameters including, but not limited to, C_{max}, T_{max}, and AUC of a single dose of MLN0128 milled API capsules administered on an empty stomach approximately 24 hours after paclitaxel infusion (Combination Arm)

3.2 Secondary Endpoints

The secondary endpoints are:

- PK parameters including, but not limited to, C_{max}, T_{max}, and AUC of a single dose of MLN0128 milled or unmilled API capsules administered on an empty stomach (Single-Agent QD and Single-Agent QW Arm)

- Rates of overall response, progression-free survival, clinical benefit responses, and detectable changes in tumor volume/size from baseline

4. STUDY DESIGN

4.1 Overview of Study Design

This study is a multicenter, open-label, phase 1 trial of MLN0128 administered orally both as a single agent and in combination with IV infusions of paclitaxel in adult patients with advanced nonhematologic malignancies for whom standard, curative, or life-prolonging anticancer treatment does not exist or is no longer effective. The study will consist of 3 arms: a Single-Agent QD Arm, a Combination Arm, and a Single-Agent QW Arm. The 3 arms will enroll in parallel and will administer study treatment in repeated 28-day cycles.

Study eligibility will be determined during the Screening period, which may last for up to 28 days before the first dose of study drug is administered. Patients who meet all eligibility criteria and provide written informed consent will be enrolled.

The Single-Agent QD Arm will test the safety, tolerability, and PK of MLN0128 milled API capsules when administered on an empty stomach and will additionally characterize the PK profile when taken with a standardized high-fat breakfast. In the same patients, the PK of MLN0128 unmilled API capsules when taken on an empty stomach will also be assessed as a point of reference for comparison of milled API capsule PK. The PK assessments will be performed during a PK Run-In period during which each patient will receive a total of three 4-mg doses of MLN0128 as described below and in Table 1-2.

- PK Run-In Visit 1: MLN0128 4-mg unmilled API capsule taken on an empty stomach.

- PK Run-In Visit 2 (24 hours [± 1 hr] after PK Visit 1): 24-hour postdose PK sample collected.

- PK Run-In Visit 3 (≥ 48 hours after PK Visit 1): MLN0128 4-mg milled API capsule taken with a standardized high-fat breakfast.

- PK Run-In Visit 4 (24 hours [± 1 hr] after PK Visit 3): 24-hour postdose PK sample collected.

- PK Run-In Visit 5 (≥ 48 hours after PK Visit 3): MLN0128 4-mg milled API capsule taken on an empty stomach.

- PK Run-In Visit 6 (24 hours [± 1 hr] after PK Visit 5): 24-hour postdose PK sample collected. Note: If scheduling permits, Visit 6 can be combined with Cycle 1 Day 1 of the Study Treatment period. That is, the 24-hour postdose PK sample for the Visit 5 PK dose can be drawn before the first administration of the patient's assigned Study Treatment dose, if the timing allows.

Each patient in the Single-Agent QD Arm will complete the PK Run-In period within 14 days before Cycle 1 Day 1 of the Study Treatment period. Study treatment for the Single-Agent QD Arm will consist of repeated 28-day cycles of oral MLN0128 milled API capsules taken on an empty stomach. The first 6 patients enrolled into the Single-Agent QD Arm Study Treatment period will receive MLN0128 at 4 mg QD. An evaluation of safety and tolerability will be conducted after these first 6 patients have completed Cycle 1 to determine the dose to be administered (see Section 6.3) during the Study Treatment period for the next patients enrolled into the Single-Agent QD Arm. Safety evaluations will continue before enrolling each subsequent cohort into the Single-Agent QD Arm. A total of 16 subjects will complete the protocol-specified PK evaluations in the Single-Agent QD Arm.

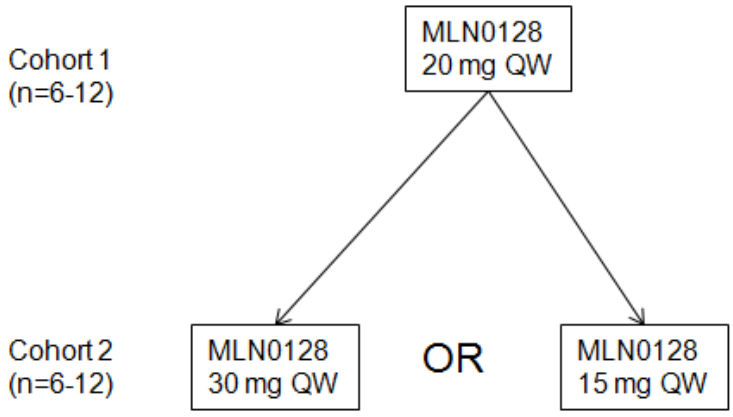
The Combination Arm will test the safety, tolerability, and PK of MLN0128 milled API capsules when administered on an empty stomach in combination with paclitaxel. Paclitaxel (80 mg/m^2) will be administered as an IV infusion on Days 1, 8 (± 1 day), and 15 (± 1 day) of each 28-day cycle according to the institution's standard clinical practice. MLN0128 will be administered QD × 3 days QW of each cycle, beginning 24 hours after completion of the

Day 1 paclitaxel infusion; ie, MLN0128 will be administered on Days 2 through 4, 9 through 11, 16 through 18, and 23 through 25 of every 28-day cycle. The starting MLN0128 dose for the Combination Arm will be 6 mg (QD × 3 days QW). Plasma samples to characterize the PK of MLN0128 will be collected on Cycle 1 Day 2.

Consistent with the Single-Agent QD Arm, an interim safety and tolerability review will be conducted for the Combination Arm after the initial cohort of 6 patients has completed Cycle 1. According to standard dose escalation rules on the basis of the safety and tolerability observed in the initial 6 evaluable patients, the dose of MLN0128 (QD × 3 days QW) for the next cohort of 6 patients will be either reduced, maintained or escalated (see Section 6.4).

The Single-Agent QW Arm will evaluate the safety, tolerability, and PK of MLN0128 milled API when administered on an empty stomach in 2 sequential cohorts, each consisting of 6 to 12 patients. Initially, 6 patients in Cohort 1 will receive 20 mg of MLN0128 capsules based on milled API once every week (QW). Serial plasma specimens will be collected for evaluation of MLN0128 PK. A safety and tolerability assessment will be performed after the last patient in the cohort completes Cycle 1. If ≥2 patients experience a dose-limiting toxicity (DLT) during Cycle 1, then the starting dose of MLN0128 milled API for the subsequent cohort (Cohort 2) will be reduced to 15 mg QW. If ≤1 patient in Cohort 1 experiences a DLT in Cycle 1, then the dose of milled MLN0128 in Cohort 2 will be increased to 30 mg QW. If the dose of MLN0128 milled API is deemed safe in any cohort based on 3+3 rules, then the cohort may be expanded to 12 patients to confirm the RP2D for single-agent MLN0128 milled API capsules when administered QW. The escalation algorithm is displayed in Figure 4-1.

Figure 4-1 MLN0128 Dose Escalation for Single-Agent QW Arm



Blood will be collected from all patients for PK analysis of MLN0128. Blood samples for all PK analyses will be collected at the time points specified in Table 1-3

Throughout the study, patient safety will be monitored through assessment of AEs clinical laboratory values, vital signs, and electrocardiograms (ECGs).

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.[8] Dose-limiting toxicities (DLTs) are defined in Section 6.2.

4.2 Number of Patients

Approximately 44 to 56 evaluable patients will be enrolled at approximately 5 study centers in the United States (US). Enrollment is defined as the time of the initiation of the first dose of study drug (ie, MLN0128 or paclitaxel, whichever is administered first).

Patients in the Single-Agent QD Arm who are withdrawn from treatment before completing per-protocol PK assessments in the PK Run-In period will be replaced.

4.3 Duration of Study

In the absence of unacceptable treatment-related toxicity or disease progression, patients may receive study 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 if, in the opinion of the investigator, the patient is benefitting from treatment.

It is anticipated that this study will last for approximately 12 months.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Age ≥ 18 years, including males and females.

2. Advanced nonhematologic malignancies, with the exception of primary brain tumor, and have failed or are not eligible for standard of care therapy. History of brain metastasis may be allowed if all the following criteria are met: brain metastases have been treated, there is no evidence of progression or hemorrhage after treatment, dexamethasone discontinued for ≥ 4 weeks before first study drug administration, and there is no ongoing requirement for dexamethasone or anti-epileptic drugs.

3. Received not more than 4 prior lines of systemic cytotoxic chemotherapy for advanced or metastatic disease.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1.

5. Adequate organ function, including the following:

    - Bone marrow reserve consistent with absolute neutrophil count (ANC) ≥ 1.5×10^9/L; platelet count ≥ 100×10^9/L; and hemoglobin ≥ 9 g/dL without transfusion in the last 2 weeks

    - Hepatic: total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN), transaminases (aspartate aminotransferase [AST]/serum glutamic oxaloacetic transaminase and alanine aminotransferase [ALT]/serum glutamic pyruvic transaminase) ≤ 2.5 × ULN (≤ 5 × ULN if liver metastases are present)

    - Renal: normal serum creatinine or calculated creatinine clearance ≥ 50 mL/min based either on Cockroft-Gault estimate (see Section 14.2) or based on urine collection (12- or 24-hour)

- Metabolic: fasting serum glucose (≤ 130 mg/dL) and fasting triglycerides ≤ 300 mg/dL

6. 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 before 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).

7. Female patients who:

   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (ie, status post-vasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

8. Ability to swallow oral medications.

9. Voluntary written consent obtained before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be use enrolled in 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. Received prior cancer therapy or other investigational therapy within 2 weeks before the first administration of study drug. For prior therapies with a half-life longer than 3 days, the interval must be at least 28 days before the first administration of study drug, and the patient must have documented disease progression.

5. Initiation of hematopoietic growth factors within 1 week before the first administration of any study drug; patients already receiving hematopoietic growth factors on a chronic basis for ≥ 4 weeks are eligible.

6. Chronic systemic corticosteroid (except inhalers) use within 1 week before the first administration of study drug. Premedication with dexamethasone before paclitaxel administration in this study is allowed. Use of low-dose glucocorticoids for replacement therapy is also allowed.

7. Manifestations of malabsorption due to prior gastrointestinal surgery, gastrointestinal disease, or for some other reason that may alter the absorption of MLN0128. In addition, patients with enteric stomata are also excluded.

8. Poorly controlled diabetes mellitus defined as glycosylated hemoglobin (HbA1c) > 7%; subjects with a history of transient glucose intolerance due to corticosteroid administration are allowed if all other eligibility criteria are met.

9. Other clinically significant comorbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study.

10. Known human immunodeficiency virus infection.

11. Pregnant (positive serum or urine pregnancy test) or breastfeeding.

12. History of any of the following within the last 6 months before administration of the first dose of study drug:

    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures
    - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia)
    - Placement of a pacemaker for control of rhythm
    - New York Heart Association Class III or IV heart failure (see Section 14.3)
    - Pulmonary embolism

13. Significant active cardiovascular or pulmonary disease before administration of the first dose of study drug, including:

    - Uncontrolled hypertension (ie, systolic blood pressure > 180 mm Hg; diastolic blood pressure > 95 mm Hg)
    - Pulmonary hypertension
    - Uncontrolled asthma or oxygen saturation < 90% by arterial blood gas analysis or pulse oximetry on room air
    - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention; or history of valve replacement
    - Medically significant (symptomatic) bradycardia

- History of arrhythmia requiring an implantable cardiac defibrillator
- Baseline prolongation of the rate-corrected QT interval (QTc; eg, repeated demonstration of QTc interval > 480 ms, or history of congenital long QT syndrome, or torsades de pointes)

14. 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.

15. **Single-Agent QD Arm patients participating in the PK Run-In (only):** patients who use proton pump inhibitors (PPIs) less than 5 days before the first MLN0128 PK Run-In dose OR use H_2 receptor antagonists within 24 hours of the first PK Run-In dose. (Note that these restrictions apply to the PK Run-In period but do not apply to the Study Treatment period for any Arm). See Section 6.7 for more information.

6. STUDY DRUG

6.1 Study Drug Administration

Millennium-sponsored drug product will be provided to the study sites. All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). In all treatment arms, study drugs will be administered during the Study Treatment period in 28-day cycles. Each patient will participate in only 1 cohort and 1 dosing schedule.

Eligible patients will report to the study site to receive their assigned study treatment on days specified in the corresponding Schedules of Events. Each patient in the Single-Agent QD Arm will complete the PK Run-In period (see Table 1-2) within 14 days before Cycle 1 Day 1 of the Study Treatment period. During the Study Treatment period for the Single-Agent QD Arm, study drug administration will consist of repeated 28-day cycles of daily oral MLN0128 milled API capsules taken on an empty stomach.

Study drug administration during the Study Treatment period for all treatment arms will follow the schedules shown in the Study Drug Dosing Diagram. MLN0128 will be administered at approximately the same time on each dosing day. On dosing days when the patient does not have a clinic visit, patients will take their assigned MLN0128 dose at home. Except as specified in Table 1-2, MLN0128 will be taken on an empty stomach. Patients should be instructed to refrain from eating and drinking (except water and prescribed medications) for 2 hours before and 1 hour after each dose. It is recommended that each dose of MLN0128 be taken with 8 ounces (240 mL) of water.

During the Study Treatment period for all treatment arms, patients will be instructed to record in their dosing diary (see the Pharmacy Manual) each MLN0128 dose they take. If severe emesis or mucositis prevents the patient from taking an MLN0128 dose, that dose will be skipped. If emesis occurs after study medication ingestion, the dose should be counted as missed and will not be re-administered, and patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diary (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses. A forgotten or missed dose of MLN0128 should be taken if it is possible to do so **within 6 hours** of the scheduled dosing time for the Single-Agent QD Arm and Combination Arm and within 12 hours of the scheduled dosing time for the Single-Agent QW Arm; otherwise, that dose should be skipped, and the next dose should be taken as scheduled. Any skipped dose should be considered a missed dose. For doses missed during the PK Run-In phase, evaluability and replacement of patients will be assessed and carried out accordingly.

All missed MLN0128 doses or doses administered within approximately 1 hour before a vomiting episode should be recorded in the electronic case report form (eCRF).

Additional information for the Combination Arm: Commercially available paclitaxel will be procured or distributed according to the Pharmacy Manual. Paclitaxel (80 mg/m^2 IV) will be administered on Days 1, 8 (± 1 day), and 15 (± 1 day) of each Study Treatment cycle. The investigator will refer to the current paclitaxel product label for the most recent instructions on drug handling, administration, risks, and potential side effects.[9, 10]

6.2 Definitions of Dose-Limiting Toxicity

Dose-limiting toxicities are defined according to the AE profile observed in Cycle 1 and the PK Run-In period as described below. All AEs should be considered possibly related to MLN0128 unless such relationship can be definitively excluded.

Toxicity will be evaluated according to NCI CTCAE (Version 4.03, effective 14 June 2010).[8] These criteria are provided in the Study Manual. Dose-limiting toxicity will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with MLN0128:

- Grade 3 or higher nonhematologic toxicity, despite adequate treatment, except for the following:
    - Grade 3 hyperglycemia lasting ≤ 14 days (all patients should receive optimal antiglycemic treatment, including insulin)
    - Grade 3 rash lasting ≤ 3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary)
- Grade 3 thrombocytopenia with hemorrhage
- Grade 4 neutropenia lasting > 7 days in the absence of growth factor support
- Grade 4 neutropenia of any duration accompanied by fever ≥ 38.5°C and/or systemic infection
- Any other ≥ Grade 4 hematologic toxicity
- Inability to administer at least 75% of planned doses of MLN0128 within Cycle 1 due to study drug-related toxicity
- Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk

Patients who experience an AE that meets the definition of a DLT during or after completing Cycle 1 should have their study drug treatment interrupted. If the event resolves to Grade 1 or baseline values within 2 weeks of interrupting planned therapy, and in the opinion of the investigator and the sponsor's project clinician the benefits of continuing treatment outweigh the risks posed by the toxicity, patients may continue study treatment with MLN0128 up to a 33% dose reduction (ie, dose reduced to 4 mg QD × 3 days) with approval of the sponsor's project clinician. If study drug dosing is delayed for more than 14 consecutive days for MLN0128-related toxicity, despite supportive treatment per standard clinical practice, or more than 2 dose reductions of MLN0128 are required, the patient will be discontinued from the study.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding the starting dose for the second cohort in the Single-Agent QW Arm and for the expansion of the second cohort in the Single-Agent QW Arm. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

6.3 Dose Escalation Plan for the Single-Agent QD Arm

All patients in the Single-Agent QD Arm will first complete the PK Run-In period before entering the Study Treatment period. During the Study Treatment period, all patients will receive MLN0128 milled API capsules.

An interim safety and tolerability review will be conducted for each Single-Agent QD Arm cohort following completion of Cycle 1 of the Study Treatment period to determine the Study Treatment dose for the next Single-Agent QD Arm cohort. Dose escalation rules for the Single-Agent QD Arm are outlined below.

The first cohort of 6 patients will receive 4 mg QD.

- If ≤ 1 DLTs occur in these 6 patients at 4 mg QD, the next 6 patients will receive 5 mg QD.
    - If ≤ 1 DLTs occur, the next 6 patients will receive 5 mg QD.
    - If ≥ 2 DLTs occur, the next 6 patients will receive 4 mg QD.
- If ≥ 2 DLTs occur in the initial 6 patients receiving 4 mg QD, the next 6 patients will receive 3 mg QD.
    - If ≤ 1 DLTs occur, the next 6 patients will receive 3 mg QD.
    - If ≥ 2 DLTs occur, enrollment in the Single Agent Arm will be closed.

6.4 Dose Escalation Plan for MLN0128 in the Combination Arm

All patients in the MLN0128 Combination Arm will receive MLN0128 milled API capsules on a dosing schedule beginning approximately 24 hours after completion of the Day 1 infusion of paclitaxel (80 mg/m^2 IV).

The first 6 patients enrolled into the Combination Arm will receive MLN0128 6 mg QD × 3 days QW beginning approximately 24 hours after completion of the Day 1 infusion of paclitaxel. An interim safety and tolerability review will be conducted after the initial cohort of 6 evaluable patients has completed Cycle 1. On the basis of the safety and tolerability observed in a minimum of 3 of the 6 evaluable patients, the MLN0128 dose administered to the next Combination Arm cohort will either be 4 mg QD × 3 days QW, 6 mg QD × 3 days QW, or 8 mg QD × 3 days QW, initiated approximately 24 hours after completion of the Day 1 infusion of paclitaxel.

If ≥ 2 DLTs occur in the 6 mg QD × 3 days QW cohort, the MLN0128 dose will be reduced to 4 mg QD × 3 days QW in the 6 patients in the next Combination Arm cohort:

- If ≤ 1 DLTs occur in the 6 patients at 4 mg QD × 3 days QW, the cohort will be expanded by enrolling 6 additional patients at 4 mg QD × 3 days QW. If ≤ 1 DLTs occur in the additional 6 patients at 4 mg QD × 3 days QW, this is the MTD.

- If ≥ 2 DLTs occur in the 6 patients at 4 mg QD × 3 days QW, the study will be stopped.

If ≤ 1 DLTs occur in the 6 mg QD × 3 days QW cohort, the MLN0128 dose will be escalated to 8 mg QD × 3 days QW in the 6 patients in the next Combination Arm cohort:

- If ≤ 1 DLTs occur in the 6 patients at 8 mg QD × 3 days QW, the cohort will be expanded by enrolling 6 additional patients at 8 mg QD × 3 days QW. If ≤ 1 DLTs occur in the additional 6 patients at 8 mg QD × 3 days QW, this is the MTD.

- If ≥ 2 DLTs occur in the 6 patients at 8 mg QD × 3 days QW, the dose will be reduced, and 6 additional patients will be enrolled at 6 mg QD × 3 days QW. If ≤ 1 DLTs occur in the additional 6 patients at 6 mg QD × 3 days QW, this is the MTD.

The decision to escalate or de-escalate the dose of MLN0128 milled API in the second cohort of the Combination Arm cohort will be based on safety, and will be informed by review of available PK data.

6.5 Dose Escalation Plan for the Single-Agent QW Arm

The starting dose of MLN0128 in the second cohort (Cohort 2) in the Single-Agent QW Arm will be based on the occurrence of DLTs in the first cohort as follows:

- If ≥ 2 patients in the first cohort (Cohort 1) of 6 patients receiving 20 mg MLN0128 QW experience DLTs during Cycle 1, then the starting dose for the subsequent cohort will be reduced to 15 mg MLN0128 QW.

- If 0 or 1 patient in the first cohort of 6 patients receiving 20 mg MLN0128 QW experiences a DLT, then the starting dose for the subsequent cohort (Cohort 2) of 6 patients will be increased to 30 mg MLN0128 QW.

The decision to escalate or de-escalate the dose of MLN0128 milled API in the second cohort (Cohort 2) in the Single-Agent QW Cohort will be based on safety, and will be informed by review of available PK data.

6.6 Dose Modification Guidelines

The investigators should try to the best of their ability to assess whether an AE is possibly related to study drug, and if so, attribute it to MLN0128 only, paclitaxel only, or MLN0128 and paclitaxel, and treat the patient accordingly. This section and Table 6-1 provide suggested guidelines for the management of various study drug-related toxicities that may occur in this study.

In general, dose modification rules when managing hematologic or nonhematologic toxicities are intended for use in a similar manner for patients enrolled in either arm. Recommendations are to be applied to patients as appropriate to their treatment assignment and symptoms.

All patients who continue to experience any toxicity (hematologic or nonhematologic) of a severity that requires > 2 dose reductions of either MLN0128 or paclitaxel (4 total), given administration of appropriate supportive care, should discontinue protocol treatment. However, if the patient has evidence of clinical benefit and is considered to possibly benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review and written approval by the project clinician. These circumstances should be discussed on a case-by-case basis. As a general rule, if a patient requires dose reduction because of a study drug-related toxicity, the drug dose may not be re-escalated.

To manage hematologic or nonhematologic toxicities that require dose reductions, the dose modifications planned for this protocol will include the following:

Paclitaxel: Paclitaxel dosing should be withheld for ≥ Grade 2 paclitaxel-related toxicities and resumed at the same dose or at a 20-mg/m^2 dose reduction depending on the timing of recovery and number of episodes that occurred (see Table 6-1). If paclitaxel dosing is delayed because of paclitaxel-related toxicities for > 21 consecutive days despite supportive treatment per standard clinical practice or > 2 dose reductions of paclitaxel (≤ 40 mg/m^2) are required, paclitaxel therapy should be stopped.

MLN0128: In general, MLN0128 dosing should be withheld for ≥ Grade 3 MLN0128-related nonhematologic toxicities. Table 6-1 provides suggested guidelines for the investigators to use along with their best judgment for an MLN0128 and/or paclitaxel dose delay and/or reduction, based on the AE observed. If MLN0128 dosing is delayed because of MLN0128-related toxicities for > 21 consecutive days despite supportive treatment per standard clinical practice or if > 2 MLN0128 dose reductions are required, stop MLN0128 (and paclitaxel therapy, if applicable), discontinue the subject from the study, and complete the end-of-study visit within 30 days of the last administration of MLN0128 or paclitaxel, whichever is discontinued last.

The decision regarding which study drug requires dose reduction will depend on the toxicity, its onset and time course, the investigator's judgment, and the actual treatment assignment of the patient. For example, hematologic toxicities and neuropathy have been related to paclitaxel but have not been a frequent or dominant toxicity associated with MLN0128. The dose of paclitaxel alone should be adjusted for hematologic toxicities or nonhematologic toxicities such as neuropathy, and the dose of MLN0128 should be reduced for nonhematologic toxicities more clearly attributed to MLN0128 (such as stomatitis, fatigue, hyperglycemia, and rash) that are not due to other comorbidities.

For the Combination Treatment Arm, as a general approach to manage taxane-related hematologic toxicities, paclitaxel should be reduced first (or delayed) before initiation of myeloid growth factors or before modification of MLN0128. To manage neutropenia attributable to paclitaxel or to the combination with MLN0128, the general goals include avoiding a reduction of the MLN0128 dose below a clinically relevant range. Given these considerations, the first intervention will be dose reduction of paclitaxel to 60 mg/m^2 (depending on the timing of recovery and number of episodes occurred). The next intervention would be to add myeloid growth factor, if appropriate. Only after interventions that include myeloid growth factor for hematological toxicity, if appropriate, would the paclitaxel dose be reduced a second time, to 40 mg/m^2.

Myeloid growth factors are not allowed to be used in Cycle 1 but may be administered per investigator discretion for supportive care to manage neutropenia events if clinically indicated. In such cases, the American Society of Clinical Oncology Guidelines and/or institutional practices and the product label should be followed. Thus, the use of myeloid growth factors as prophylaxis is not mandated, but as indicated in Table 6-1, is strongly encouraged if appropriate as an intervention step at the repeat occurrence of neutropenia requiring dose modification. Short-acting myeloid growth factors are preferred, and they should be discontinued for an appropriate number of days before restarting protocol treatment.

Table 6-1 Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Absolute Neutrophil Count (ANC)		
Grade 2 (< 1500-1000/mm^3)	No change. Continue MLN0128 at same dose and schedule.	No change. Continue paclitaxel at same dose and schedule. For ANC ≤ 1500/mm^3, consider the use of prophylactic myeloid growth factors (ie, GCSF): • Start 1 or 2 days after paclitaxel infusion and use for 2 to 6 days according to patient's need, at physician discretion, and to avoid dose reduction. • Growth factor should not be given on the same day as paclitaxel infusion. • GCSF is preferred over pegfilgrastim because of the weekly dosing of paclitaxel in this study.
Grade 3 (< 1000-500/mm^3)	No change. Continue MLN0128 at same dose and schedule. Consider use of prophylactic myeloid growth factor support per guidelines above.	Hold paclitaxel until ANC > 1000/mm^3. Resume paclitaxel based on timing of recovery and number of previous episodes: • ≤ 2 weeks of interrupting planned therapy: o First episode: no change to paclitaxel dose. o ≥ Second episode: reduce paclitaxel by 25% for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue patient from study. Consider use of prophylactic myeloid growth factor support per guidelines above.

Table 6-1 Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Grade 4 (< 500/mm^3)	Hold MLN0128 until ANC > 1000/mm^3. Resume MLN0128 based on timing of recovery: • ≤ 1 week: no change to MLN0128 dose. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue patient from study. Consider use of prophylactic myeloid growth factor support per guidelines above.	Hold paclitaxel until ANC > 1000/mm^3. Resume paclitaxel based on timing of recovery and number of previous episodes: • ≤ 2 weeks of interrupting planned therapy: o First episode: no change to paclitaxel dose. o ≥ Second episode: reduce paclitaxel by 25% for all subsequent cycles. • 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue patient from study. Consider use of prophylactic myeloid growth factor support per guidelines above.
Thrombocytopenia		
Grade 1 (≥ 75,000/mm^3)	No change. Continue MLN0128 at same dose and schedule.	No change. Continue paclitaxel at same dose and schedule.
Grade 2 (50-74,999/mm^3)	No change. Continue MLN0128 at same dose and schedule	Hold paclitaxel until platelets > 75,000/mm^3. Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • ≤ 1 week: no change to paclitaxel. • > 1 but ≤ 2 weeks of interrupting planned therapy: reduce paclitaxel by 25% for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue patient from study.
Grade 3 (25-44,999/mm^3)	Hold MLN0128 until platelets > 75,000/mm^3. Resume MLN0128 based on timing of recovery within 2 weeks: • ≤ 1 week: no change to MLN0128 dose. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue patient from study. Platelet transfusions in the absence of bleeding should not be administered.	Hold paclitaxel until platelets > 75,000/mm^3. Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • ≤ 1 week: no change to paclitaxel. • > 1 but ≤ 2 weeks of interrupting planned therapy: reduce paclitaxel by 25% for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue patient from study. Platelet transfusions in the absence of bleeding should not be administered.

Table 6-1 Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Grade 4 ($< 25{,}000/mm^3$)	Hold MLN0128 until platelets $\geq 75{,}000/mm^3$. Resume MLN0128 according to the number of episodes that are resolved to Grade ≤ 1 or baseline values within 2 weeks: • First episode: resume MLN0128 at same dose and schedule. • Second episode: reduce MLN0128 to the next lower dose for all subsequent cycles. • Third episode: reduce MLN0128 to the next lower dose from the first reduced dose for all subsequent cycles. • Fourth episode: stop MLN0128 and discontinue patient from study. Platelet transfusions should be administered prophylactically if platelets are $\leq 10{,}000/mm^3$ or as clinically indicated if there is bleeding.	Hold paclitaxel until platelets $\geq 75{,}000/mm^3$. Resume paclitaxel according to the number of episodes that are resolved to ≤ Grade 1 or baseline values within 2 weeks: • First episode: reduce paclitaxel by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • Second episode: reduce paclitaxel by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • Third episode: reduce paclitaxel by 50% from starting dose (40 mg/m^2) for all subsequent cycles. • Fourth episode: stop paclitaxel and discontinue patient from study. Platelet transfusions should be administered prophylactically if platelets are $\leq 10{,}000/mm^3$ or as clinically indicated if there is bleeding.
Hepatic		
Grade 1	No change. Continue MLN0128 at the same dose and schedule.	No change. Continue paclitaxel at the same dose and schedule.
Grade 2	Hold MLN0128 until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks. Resume MLN0128 based on timing of recovery: • ≤ 1 week: no change to MLN0128 dose. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue patient from study. A rise in indirect bilirubin with a normal direct bilirubin believed to be attributable to Gilbert's disease does not require a change or hold in MLN0128 dosing. Gilbert's disease should be documented in the patient's medical history eCRF page.	Hold paclitaxel until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks of interrupting planned therapy. Resume paclitaxel based on timing of recovery: • ≤ 1 week: no change to paclitaxel dose. • > 1 but ≤ 2 weeks of interrupting planned therapy: reduce paclitaxel dose by 25% for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue patient from study.

Table 6-1 Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
≥ Grade 3	Hold MLN0128 until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks. Resume MLN0128 according to the number of episodes that are resolved to ≤ Grade 1 or baseline values: • First episode: resume MLN0128 at the same dose and schedule. • Second episode: reduce MLN0128 to the next lower dose for all subsequent cycles. • Third episode: reduce MLN0128 to the next lower dose from the reduced dose for all subsequent cycles. • Fourth episode: stop MLN0128 and discontinue patient from study.	Hold paclitaxel until LFTs improve to ≤ Grade 1 or baseline values within 2 weeks of interrupting planned therapy. Resume paclitaxel according to the number of episodes that are resolved to ≤ Grade 1 or baseline: • First episode: reduce paclitaxel dose by 25% (60 mg/m^2) from starting dose for all subsequent cycles. • Second episode: reduce paclitaxel dose by 25% (60 mg/m^2) from starting dose for all subsequent cycles. • Third episode: reduce paclitaxel dose by 50% (45 mg/m^2) from starting dose for all subsequent cycles. • Fourth episode: stop paclitaxel and discontinue patient from study.
Renal (Creatinine)		
Grade 1 (> ULN-1.5 × ULN or > 1-1.5 × baseline)	No change. Continue MLN0128 at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, and creatinine	No change. Continue paclitaxel at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, and creatinine

Table 6-1 Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Grade 2 (> 1.5-3 × ULN or > 1.5-3.0 × baseline)	Hold MLN0128 until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, and creatinine Consider IV hydration. Resume MLN0128 based on timing of recovery: • ≤ 1 week: no change to MLN0128 dose. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue patient from study.	Hold paclitaxel until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks of interrupting planned therapy. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, and creatinine Consider IV hydration. Resume paclitaxel at the same dose and schedule.
≥ Grade 3 (> 3-6 × ULN/ >3 baseline or > 6 × ULN)	Hold MLN0128 until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, and creatinine Consider IV hydration. Resume MLN0128 based on timing of recovery: • ≤ 1 week: no change to MLN0128 dose. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue patient from study.	Hold paclitaxel until creatinine improves to ≤ Grade 1 or baseline values ≤ 2 weeks of interrupting planned therapy. Collect the following tests to help identify cause of renal dysfunction: • Chemistry 7 • Urinalysis • 12-hour urine collection • Spot urine for electrolytes, protein, and creatinine Consider IV hydration. Resume paclitaxel based on timing of recovery: • ≤ 1 week: no change to paclitaxel dose. • > 1 but ≤ 2 weeks of interrupting planned therapy: reduce paclitaxel dose by 25% for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue patient from study.

Table 6-1 Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Peripheral Neuropathy		
≤ Grade 2	No change. Continue MLN0128 at same dose and schedule.	No change. Continue paclitaxel at same dose and schedule.
≥ Grade 3	Continue MLN0128 during the first week when paclitaxel treatment is interrupted. • If peripheral neuropathy does not improve to ≤ Grade 2 after 1 week of paclitaxel treatment interruption, hold MLN0128 for 1 week. • Resume MLN0128 at the next lower dose if the event recovers to ≤ Grade 2 after 1 week of MLN0128 interruption (2 weeks of paclitaxel interruption). • Stop MLN0128 if the event does not recover to ≤ Grade 2 after 1 week of MLN0128 interruption (2 weeks of paclitaxel interruption).	Hold planned paclitaxel for 1 week to see if peripheral neuropathy improves to ≤ Grade 2. • Reduce paclitaxel dose by 25% for all subsequent cycles if peripheral neuropathy improves to ≤ Grade 2 after 1 week of paclitaxel planned treatment interruption. • If peripheral neuropathy does not improve to ≤ Grade 2 after 1 week of planned paclitaxel treatment interruption, continue to hold paclitaxel treatment while MLN0128 treatment is held. • Resume paclitaxel by 25% dose reduction for all subsequent cycles if event recovers to ≤ Grade 2 after 2 weeks of paclitaxel interruption (1 week of MLN0128 interruption). • Stop paclitaxel if the event does not recover to ≤ Grade 2 after 2 weeks of planned paclitaxel treatment interruption (1 week of MLN0128 interruption).
Hyperglycemia		
≤ Grade 2 (ULN-250 mg/dL)	Continue MLN0128 at same dose and schedule. Refer to Section 6.10.1 for guidelines on hyperglycemia management.	Continue paclitaxel at same dose and schedule. Refer to Section 6.10.1 for guidelines on hyperglycemia management.
≥ Grade 3 (> 250 mg/dL)	Hold MLN0128 until hyperglycemia improves to ≤ Grade 2. Refer to Section 6.10.1 for guidelines on hyperglycemia management. Optimize hyperglycemia therapy and resume MLN0128 based on timing of recovery: • ≤ 1 week: resume MLN0128 at same dose and schedule. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose. • > 2 weeks: stop MLN0128 and discontinue patient from study.	Continue paclitaxel at same dose and schedule. Refer to Section 6.10.1 for guidelines on hyperglycemia management.

Table 6-1 Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Rash		
≤ Grade 2	Continue MLN0128 at same dose and schedule. Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	Continue paclitaxel at same dose and schedule. Consider treatment with topical steroid cream/ointment and/or oral antihistamines.
≥ Grade 3	Hold MLN0128 until rash improves to ≤ Grade 2. Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or oral pulse steroids. Refer to Section 6.10.4 for guidelines on management of rash. Resume MLN0128 based on timing of recovery: • ≤ 2 weeks: reduce MLN0128 to the next lower dose level. • > 2 weeks: stop MLN0128 and paclitaxel and discontinue patient from study.	Continue paclitaxel at same dose and schedule. Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or oral pulse steroids.

Abbreviations: ANC = absolute neutrophil count; eCRF = case report form; GCSF = granulocyte-colony stimulating factor; IV = intravenous(ly); LFT = liver function test; ULN = upper limit of the normal range.

For the Single-Agent QW Arm, MLN0128 administration should be withheld for treatment-related adverse events that are Grade 3 or higher, despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 or to baseline values within 3 weeks of interrupting treatment, then the patient may resume study treatment at a dose reduced by 1 level (see Table 6-2). If a patient does not tolerate 15 mg, then the investigator and the project clinician should discuss whether the patient would benefit from a further dose reduction.

Table 6-2 Dose Modifications for Single-Agent QW Arm

Dose Level	Dose Regimen	MLN0128 Capsules: Number and Strength
0	30 mg QW	Six 5-mg capsules
–1	20 mg QW	Four 5-mg capsules
–2	15 mg QW	Three 5-mg capsule
–3	10 mg QW	Two 5-mg capsules

Abbreviations: QW = once weekly.

6.7 Excluded Concomitant Medications, Foods, and Procedures

6.7.1 All Treatment Arms

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient as of the first study drug administration through 30 days after the last dose will be recorded on the designated eCRF.

The following medications, therapies, and foods are prohibited during the study, except as indicated below:

- Other investigational agents or mTOR inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery (patients can have palliative radiation or surgery during the study for pre-existing lesions).
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of an MLN0128-related AE (eg, rash). Premedication with dexamethasone before paclitaxel administration in this study is allowed. Use of low-dose glucocorticoids for replacement therapy is also allowed.
- Anti-epileptic drugs for patients with a history of treated brain metastasis.
- Anti-emetic drugs associated with a significant risk for QT prolongation, including ondansetron.
- Strong cytochrome CYP1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator (refer to Section 14.4 for a list of these agents). Alternative treatments, if available, should be considered.
- No dietary restrictions will be imposed on study patients.
- Administration of any proton pump inhibitor (PPI) is not permitted during the PK Run-In period of the Single-Agent QD and Single-Agent QW Arms. Patients in the Single-Agent QD and Single-Agent QW Arms who receive PPI therapy before enrollment must stop using the PPI for 5 days before their first PK Run-In dose until completion of PK Visit 6. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole. Note that this restriction does not apply to the Study Treatment period for any treatment arm.

The use of an H_2 receptor antagonist is not permitted during the PK Run-In period of the Single-Agent QD Arm, beginning 24 hours before administration of the first PK Run-In dose through completion of PK Visit 6. Examples of H_2 receptor antagonists include ranitidine, famotidine, and nizatidine. Note that this restriction does not apply to the Study Treatment period for any treatment arm. During the Study Treatment period, H_2 receptor antagonists may be allowed, if needed, provided that the histamine H_2 receptor antagonist is not taken within 12 hours before and within 6 hours after study drug administration. However, cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first-choice H_2 receptor antagonist (refer to Section 14.4).

Treatment with neutralizing antacids (eg, Maalox Max, calcium carbonate) is not permitted within 4 hours before and within 6 hours after receiving a dose of MLN0128.

6.7.2 Combination Arm

Benzodiazepines are to be avoided in patients receiving paclitaxel. Please refer to the most recent paclitaxel US Prescribing Information (USPI) for information on medications that are prohibited in patients receiving paclitaxel.

6.8 Permitted Concomitant Medications and Procedures

6.8.1 All Treatment Arms

Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose of study drug, as needed throughout the study before each dosing, and as clinically indicated per standard practice.

Concomitant treatment with bisphosphonates is permitted for treatment of osteoporosis or management of existing bone metastasis if initiated at least 4 weeks before administration of the first dose of study drug. Bisphosphonates should be given after Cycle 1 to minimize confounding factors that may contribute to potential drug-related toxicities.

Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

6.8.2 Combination Arm

Premedication with corticosteroids, diphenhydramine, or H2 receptor antagonists is permitted before each treatment with paclitaxel.

6.9 Precautions and Restrictions

6.9.1 All Treatment Arms

No dietary restrictions will be imposed on study patients. Patients will be instructed to fast overnight for daily glucose monitoring (refer to Section 7.4.16).

Patients who show evidence of hyperglycemia during the study should be encouraged to follow a low carbohydrate diet.

It is not known what effects MLN0128 has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant. Nonsterilized patients in the reproductive age group should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal,

postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.9.2 Combination Arm

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. Premedication to prevent hypersensitivity reactions to paclitaxel should be administered per standard practice guidelines and the current paclitaxel USPI. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

To monitor the occurrence of bone marrow suppression in patients receiving paclitaxel—primarily neutropenia, which may be severe and result in infection—it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel. Patients should not be retreated with subsequent cycles unless neutrophils are > 1500 cells/mm^3 and platelets are > 100,000 cells/mm^3.

Please refer to the most recent paclitaxel USPI for additional information on precautions and restrictions associated with paclitaxel administration.

6.10 Management of Clinical Events: All Treatment Arms

6.10.1 Management of Hyperglycemia

In addition to obtaining fasting serum glucose levels at the clinic visits as outlined in the Schedules of Events, all patients will be provided with a glucometer and trained in its use to monitor their daily predose fasting blood glucose (FBG) levels at home (see Section 7.4.16). Patients will be instructed to notify the study staff immediately of any abnormal readings (ie, ≥ 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 irregularities in the FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home fasting glucose testing may be reduced to twice weekly if the investigator approves. Patients will continue to notify the investigator of FBG levels ≥ 150 mg/dL, and if blood glucose levels are not well controlled, or if they require either oral hypoglycemic agents or insulin to control blood glucose levels, then the

frequency of in-home testing of FBG levels will be reinstated to daily. Guidelines for management of hyperglycemia are presented in Table 6-3.

Table 6-3 Management of Hyperglycemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	FBG > ULN-160 mg/dL	Continue close monitoring of blood glucose. Initiate oral hypoglycemic agent.	None
2	FBG > 160-250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥ 3	FBG > 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 to the next lower dose. • > 2 weeks: stop MLN0128 and discontinue patient 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. • Recommend lifestyle modifications, as appropriate (balanced diet, limited alcohol consumption, increased 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. • FBG levels ≥ 150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.			

Abbreviations: FBG = fasting blood glucose; HbA1c = glycosylated hemoglobin; ULN = upper limit of the normal range.

If any fasting serum glucose reading performed at the site indicates hyperglycemia (> ULN or ≥ 110 mg/dL), the study staff should first confirm that the patient was fasting at the time of the blood draw (ie, nothing by mouth for at least 8 hours before). To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines are provided to aid the investigator in initiating antiglycemic therapies.

In the clinical experience with MLN0128, most episodes of hyperglycemia observed have been Grade 1 or Grade 2 and have responded quickly to oral metformin. Hyperglycemia has not been dose limiting since instituting a standard regimen for early treatment of hyperglycemia. All patients developing hyperglycemia on the study should have their

glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of patients who develop Grade 1 hyperglycemia (FBG > ULN ≤ 160 mg/dL) or consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with ≥ Grade 2 hyperglycemia (FBG > 160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated while continuing on MLN0128 treatment. The investigator should consult an endocrinologist if needed to aid in optimizing the hyperglycemia treatment plan for the patient.

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

6.10.2 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided in Table 6-4.

Table 6-4 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 ≥ 500 mg/dL should be treated urgently because of the risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
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 the next lower dose.
4	Cholesterol: > 500 mg/dL Triglycerides: > 1000 mg/dL	Same as for Grade 2	Discontinue treatment.

Prevention/Prophylaxis

- Lifestyle modifications, as appropriate (balanced diet, limited consumption of alcoholic beverages, increased physical activity).

Abbreviations: ULN = upper limit of the normal range.

6.10.3 Management of Oral Mucositis

Guidance for the management of oral mucositis is provided in Table 6-5.

Table 6-5 Management of Oral Mucositis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic or mild symptoms	Nonalcoholic mouthwash or 0.9% saltwater 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 intralesional corticosteroids.	Hold dose until recovery to ≤ Grade 1, then restart with the next lower dose.
4	Life-threatening consequences	Same as for Grade 2; consider intralesional corticosteroids.	Discontinue treatment.

Prevention/Prophylaxis

- Consider initiation of a nonalcoholic mouthwash or 0.9% saltwater rinses 4 to 6 times daily with start of therapy before signs of mucositis develop.
- Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

6.10.4 Management of Rash

Guidance for management of rash is provided in Table 6-6.

Table 6-6 Management of Rash

Grade	Description	Treatment	MLN0128 Dose Modification
≤ 2	Macules/papules covering ≤ 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	None
≥ 3	Macules/papules covering > 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or pulsed steroids.	Hold until ≤ Grade 2; resume MLN0128 based on timing of recovery: • ≤ 2 weeks: reduce MLN0128 to the next lower dose. • > 2 weeks: discontinue MLN0128 treatment.

6.10.5 Management of Nausea and/or Vomiting

Guidance for the management of nausea and/or vomiting is provided in Table 6-7.

Table 6-7 Management of Nausea and/or Vomiting

Grade	Description	Treatment	MLN0128 Dose Modification
≤ 2	Loss of appetite with or without decreased oral intake; 1to 5 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; consider IV fluid hydration.	None
≥ 3	Inadequate oral intake; ≥ 6 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; initiate tube feeding, IVF, or TPN.	Hold until ≤ Grade 1; resume MLN0128 without dose modification.
Prevention/Prophylaxis			
Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before each dose of MLN0128 as needed throughout the study.			

Abbreviations: IV = intravenous(ly); IVF = intravenous fluids; TPN = total parenteral nutrition.

6.10.6 Management of Non-infectious Pneumonitis

Guidance for the management of pneumonitis is provided in Table 6-8.

Table 6-8 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 activities of daily living	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt MLN0128 treatment: • When symptoms ≤ Grade 1, re-initiate MLN0128 treatment with a 25% dose reduction.[a] • If no recovery within 4 weeks, then discontinue MLN0128 treatment.
3	Symptomatic: Interfering with activities of daily living; Requires administration of oxygen	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt MLN0128 treatment until symptoms resolve to ≤ Grade 1. • Consider re-initiating MLN0128 treatment with a 25% dose reduction.[a] • 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.

Abbreviation: QD = once daily; QD × 5D = once daily for 5 days each week.

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

6.11 Management of Clinical Events: Combination Arm

Please refer to the most recent paclitaxel USPI for more information on the management of clinical events in patients receiving paclitaxel.

6.12 Blinding and Unblinding

This is an open-label study; no blinding methods will be used.

6.13 Description of Investigational Agents

Upon receipt of drug supply, contents must be verified promptly and the proper contacts notified of any discrepancies or damages as described in the Study/Pharmacy Manual.

MLN0128 will be supplied as capsules for oral administration. MLN0128 is available in 3 dose strengths—1 mg, 3 mg, and 5 mg—each containing 1 mg, 3 mg, and 5 mg of

MLN0128, respectively, in addition to the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant), and hard gelatin capsule.

All 3 dose strengths are formulated into size 2 capsules, and each dose strength is differentiated by color, as listed below:

- 1-mg MLN0128 capsules: white opaque color
- 3-mg MLN0128 capsules: Swedish orange opaque color
- 5-mg MLN0128 capsules: gray opaque color

Paclitaxel is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the Pharmacy Manual. Please refer to the most recent paclitaxel USPI for more information regarding paclitaxel.

6.14 Preparation, Reconstitution, and Dispensation

MLN0128 study drug will be provided in 60-cc high-density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seals. MLN0128 will be dispensed with dosing instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

Both study drugs in this study are anticancer drugs; as with other potentially toxic compounds, caution should be exercised when handling these agents.

6.15 Packaging and Labeling

MLN0128 study drug will be provided by Millennium. MLN0128 capsules are packaged in 60-cc HDPE bottles with polypropylene, child-resistant caps and induction seals. For all 3 dose strengths, each bottle contains 30 capsules and will have a label containing pertinent study information, country-specific requirements, and a caution statement.

Supplies of the MLN0128 milled API capsules will be accompanied by a new label to differentiate them from the existing supplies of the MLN0128 unmilled API capsules.

Paclitaxel may be supplied either by the site or from commercial sources. When provided by Millennium, paclitaxel will be appropriately labeled in compliance with local and regional regulations.

6.16 Storage, Handling, and Accountability

Paclitaxel should be stored according to instructions provided in the manufacturer's package insert.[9, 10]

Upon receipt at the investigative site, MLN0128 study drug should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F-86°F). All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All study drug should be used before the retest expiry date. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

A drug dispensing log, including records of drug received from the sponsor and MLN0128 drug dispensed to the patients, will be provided and kept at the study site.

Because MLN0128 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will be given clear dosing instructions from the investigator for home storage and administration of MLN0128 capsules, including the requirement that the capsules must be stored in their original containers and that the capsules are to be swallowed whole and not chewed or manipulated in any way. Patients will also receive diary cards to record dosing compliance with their MLN0128 treatment assignment, with instructions for their completion. Patients will be instructed to return any unused MLN0128 study drug in the original packaging along with their completed diary cards at the appropriate visits.

Please refer to the Study Manual and the Pharmacy Manual for additional instructions.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, and other third-party vendors may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

Treatment group assignments in this open-label study will be at the discretion of the investigator and based on cohort availability.

7.4 Study Procedures

Refer to the Schedules of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.10.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedules of Events.

7.4.5 Patient Height and Weight

Height will be measured only during screening. Weight will be measured at the times specified in the Schedules of Events.

7.4.6 Vital Signs

Vital signs will be assessed at the times specified in the Schedules of Events.

7.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and within 3 days before the first dose of study drug (ie, Visit 1 of the PK Run-In period for patients in the Single-Agent QD Arm, and Cycle 1 Day 1 for patients in the Combination Arm and Single-Agent QW Arm). The results from these tests must be available and negative before the first dose of study drug is administered. If the serum pregnancy results will not be available before the first dose of study drug, a urine pregnancy test may be performed.

7.4.8 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status (refer to Section 14.1) will be assessed at the times specified in the Schedules of Events.

7.4.9 Multiple Gated Acquisition Scan and/or Echocardiogram

A MUGA scan or ECHO will be administered at the time points specified in the Schedules of Events.

7.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF according to the Schedules of events. See Section 6.7 and Section 6.8 for medications and therapies that are prohibited or allowed during the study.

7.4.11 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedules of Events. Refer to Section 9 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.12 Enrollment

A subject is considered to be enrolled in the study when the first dose of any study drug (ie, MLN0128 or paclitaxel) is administered. Procedures for completing the enrollment information are described in the Study Manual.

7.4.13 Electrocardiogram

A single, 12-lead ECG will be administered at the time points specified in the Schedules of Events. Additional ECGs may be obtained as clinically indicated.

7.4.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the Study Manual and/or Laboratory Manual. Clinical laboratory evaluations will be performed as outlined below.

Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedules of Events. Results of hematology and clinical chemistry safety labs must be available and reviewed by the investigator before enrollment and initial administration of any study drug.

Hematology

A blood sample for complete blood count with platelet count and white blood cell (WBC) count with differential will be obtained at the times specified in the Schedules of Events. The hematology panel includes the following:

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (ANC)

Coagulation

A blood sample for coagulation tests will be obtained at the times specified in the Schedules of Events. The coagulation panel includes the following:

- Activated partial thromboplastin time (aPTT)
- Prothrombin time/international normalized ratio (PT/INR)

Clinical Chemistry

A blood sample for the clinical chemistry panel will be obtained at the times specified in the Schedules of Events. The clinical chemistry panel includes the following:

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium
- Amylase
- HbA1c (*only at the times specified in the Schedules of Events*)

Urinalysis

Urine samples for urinalysis will be obtained at the times points specified in the Schedules of Events. Urinalysis will include macroscopic assessment of the amount of protein, glucose, WBCs, and blood if they are present (levels should be recorded if available) and microscopic analysis if abnormality is noted. The urinalysis panel includes the following:

- Turbidity and color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Occult blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes

Fasting Lipid Profile

Prospective monitoring for hyperlipidemia will be managed through fasting lipid testing at the time points specified in the Schedules of Events. Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for each of these measurements. The fasting lipid profile includes the following:

- Total cholesterol
- Triglycerides
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)

7.4.15 Fasting Serum Glucose

Fasting serum glucose will be measured at the time points specified in the Schedules of Events before administration of MLN0128, and at other times at the discretion of the investigator. Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for each of these measurements.

7.4.16 In-Home Daily Fasting Glucose Monitoring

Patients will be instructed to complete daily glucose monitoring at home after fasting overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for each of these measurements. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded into source documents. On the basis of investigator judgment, and after 2 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, patients will continue to notify the investigator of FBG levels that exceed 150 mg/dL. If blood glucose levels are not well controlled at any time during the study (see Section 6.10.1), or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, in-home testing of FBG levels will be resumed daily with the provided glucometer. On study visit days where fasting glucose is assessed in the clinic, the in-home daily fasting glucose monitoring does not need to be completed.

7.4.17 DNA Measurements

CCI

[redacted]

7.4.18 Disease Assessment

Patients will undergo a computed tomography (CT) scan (with contrast) as appropriate to monitor and assess disease progression. Investigators will assess patients' disease status using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1), where measureable disease is defined as ≥ 1 extraosseous lesion that can be accurately measured in at least 1 dimension.[(11)] Specific disease sites that cannot be adequately imaged by CT may be documented by magnetic resonance imaging (MRI). Anatomical measurements will be collected at baseline and at each subsequent evaluation for each target lesion using an imaging modality consistent with that used at screening. The same method (CT with contrast, MRI, or bone scan) must be consistently used on a patient throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI.

Objective assessments will be performed at each time point as described in the Schedules of Events. When possible, the same qualified physician will interpret results to reduce variability.

Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents. The sponsor may request electronic images for those patients who demonstrate a response.

7.4.19 Pharmacokinetic Measurements

Serial blood samples for PK analysis of MLN0128 will be collected at the time points specified in the Pharmacokinetic Sample Breakdown tables. The dates and exact times of administration of MLN0128 before collection of the blood sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded on the eCRF.

7.5 Completion of Treatment

Patients will be considered to have completed treatment if they discontinue treatment with study drug for any of the reasons outlined in Section 7.6.

The maximum duration of treatment for patients will be 12 months unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued treatment beyond 12 months.

Patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section 7.6.

7.6 Discontinuation of Treatment With Study Drug, and Patient Replacement

Treatment with study drug may also be discontinued for any of the following reasons:

- Adverse event
- Protocol violation
- Progressive disease
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

Once study drug has been discontinued, all study procedures outlined for the End of Treatment visit will be completed as specified in the Schedules of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than progressive disease before completing the full treatment course; these will remain in the study for posttreatment assessments as outlined in the Schedules of Events until disease progression occurs.

Patients in the Single-Agent QD Arm who are withdrawn from treatment before completing per-protocol PK assessments in the PK Run-In period will be replaced. In addition, patients in the Single-Agent QD Arm who miss a dose (see Section 6.1) or experience emesis within 8 hours of dosing before completing per-protocol PK assessments in the PK Run-In period will be replaced (but not removed from treatment) to achieve a sample size of 16 subjects completing the protocol-specified PK evaluations (see Section 8.1.1). Patients in all treatment arms who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

7.7 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Patients will receive a sufficient quantity of MLN0128 for each treatment cycle and a diary in which to record their dosing. The study center staff will check the patient's diary versus the patient's supply of remaining MLN0128 at each study visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan will be developed and finalized before database lock.

8.1.1 Determination of Sample Size

Each subject will participate in only 1 dose cohort.

The within-subject coefficient of variation for $AUC_{0\text{-last}}$ was estimated to be 39% on the basis of preliminary PK data from Cycle 1 Day 1 and Cycle 2 Day 1 from Study INK128-001. Assuming a geometric mean AUC ratio of 1, with a sample size of 16, the 2-sided 90% CI for the geometric mean AUC ratio is expected to be (0.796, 1.257).

On the basis of these calculations, a sample size of 16 subjects completing the protocol-specified PK evaluations in the Single-Agent QD Arm has been selected to enable adequate precision in the estimation of the geometric mean ratios.

In the Combination Arm, 6 patients will be enrolled in the first cohort (6 mg QD × 3 days QW), and another 6 patients will be enrolled in the second cohort (either 4 mg QD × 3 days QW or 8 mg QD × 3 days QW). Any cohort may be expanded up to 12 patients for confirmation of RP2Ds for MLN0128 milled API capsules when administered QD × 3 days

QW in combination with paclitaxel. The number of patients is based on clinical considerations.

For the Single-Agent QW Arm, 6 patients will be enrolled in the first cohort (20 mg QW), and another 6 patients will be enrolled in the second cohort (either 15 or 30 mg QW). Any cohort may be expanded up to 12 patients for confirmation of RP2Ds for MLN0128 milled API capsules when administered QW. The number of patients is based on clinical considerations.

8.1.2 Randomization and Stratification

This study will not require randomization or stratification.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: patients who receive at least 1 dose of study drug will be included in all safety analyses and efficacy analyses.
- PK population: patients with sufficient dosing and PK data to reliably estimate PK parameters will be included in the PK analyses.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be presented in data listings and tabulations. No imputation of values for missing data will be performed. The relevance of missing sample data will be assessed.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

Data listings will present the tumor measurements from CT or MRI (including changes from baseline), disease response category (ie, complete response, partial response, and stable

disease), overall response, duration of response, and duration of stable disease or other appropriate measures of efficacy.

8.1.7 Pharmacokinetic Analysis

Single-dose PK parameters will be calculated for MLN0128 by noncompartmental analysis as permitted by the data. These parameters will include, but will not be limited to, C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2}$, and apparent oral clearance. These parameters will be summarized by treatment arm (Single-Agent QD, Combination, or Single-Agent QW), MLN0218 API (milled vs unmilled) and dosing condition (dosing on an empty stomach vs following a standardized meal) as appropriate. The following statistical analyses will be performed on the data collected during the PK Run-In period of the Single-Agent QD Arm:

- An analysis of variance will be performed with log-transformed C_{max} and $AUC_{0\text{-last}}$ as the dependent variables, treatment as the fixed effect, and patient as the random effect.

- Least-square mean ratios between the treatment states (MLN0128 dosed with high-fat breakfast [Test]) versus MLN0128 dosed on an empty stomach [Reference]) or (MLN0128 milled API capsules [Test] versus MLN0128 unmilled API capsules [Reference]) will be calculated along with 90% confidence intervals (CIs).

8.1.8 Safety Analysis

All safety analyses will be performed using the Safety population.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the Safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- TEAEs

- Drug-related TEAEs

- Grade 3 or higher TEAEs
- Grade 3 or higher drug-related TEAEs
- The most commonly reported TEAEs
- SAEs

The most commonly reported TEAEs will be tabulated by MedDRA Preferred Term.

A listing of deaths within 30 days of the last dose of study drug and TEAEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters and the change from baseline in clinical laboratory parameters will be presented at each scheduled time point. Mean laboratory values over time may be plotted for key laboratory parameters. Shift tables based on changes in NCI CTCAE grade from baseline to the worst postbaseline value for laboratory parameters will be generated.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be presented at each scheduled time point.

Concomitant medications will be summarized according to World Health Organization drug dictionary preferred term.

Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile of MLN0128 in combination with paclitaxel or single-agent MLN0128.

Electrocardiogram Analysis

A summary of ECG abnormalities will be presented at each scheduled time point. Descriptive statistics for ECG intervals (QT, electrocardiograph with Fridericia correction [QTcF], PR, QRS, and ventricular rate) and changes from baseline will be presented at each scheduled time point.

8.1.9 Interim Analysis

No formal interim analysis is planned for this study.

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

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

All AEs spontaneously reported by the patient 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

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given 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 4.03, effective date 14 June 2010.[8] 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

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

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.
- 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 administration of the last dose of study drug and recorded in the eCRF. 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 are 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 patient becomes pregnant during the male patient'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. ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

10.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

10.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

10.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

10.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

10.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

10.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

10.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

10.10 Investigator and Site Responsibility for Drug Accountability

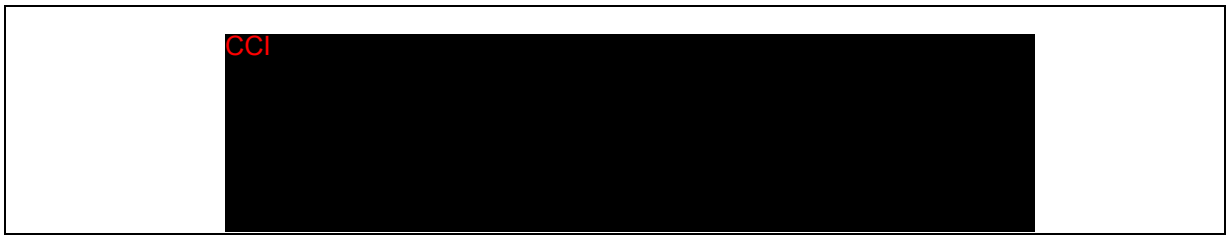
Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

10.11 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 CCI (see below) and report the event. Whenever possible, the associated product should be

maintained in accordance with the label instructions pending further guidance from a Millennium 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 sent to CCI (refer to Section 9.2).

10.12 Closure of the Study

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend, or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. If any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

10.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

11. USE OF INFORMATION

All information regarding MLN0128 supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN0128 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

12. INVESTIGATOR AGREEMENT

I have read Protocol MLN0128-1004 Amendment 3: A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies.

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

13. REFERENCES

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14. APPENDICES

14.1 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
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, et al. 1982.[12]

14.2 Cockroft-Gault Equation

$$\text{Creatinine Clearance} = \frac{0.85\,(140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\frac{0.85\,(140 - \text{age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. 1976.[13]

14.3 New York Heart Association Classification of Cardiac Disease

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

Source: The Criteria Committee of New York Heart Association. 1994.[14]

14.4 List of Relevant Cytochrome P450 Inhibitors and Clinically Significant Enzyme Inducers

Moderate CYP1A2 Inhibitors		
cimetidine	methoxsalen	
Strong CYP1A2 Inhibitors		
fluvoxamine	Ciprofloxacin	
Clinically Significant Enzyme Inducers		
carbamazepine	Rifabutin	St. John's wort
phenobarbital	Rifampin	phenytoin
rifapentine		

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.
Note that these lists are not exhaustive.

14.5 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

Clinical Study Protocol MLN0128-1004 is being amended to provide clarifications and corrections to procedures in the Schedules of Events. Additionally, this amendment clarifies that patients taking low-dose glucocorticoids for replacement therapy may be enrolled in the study. A clarification is also being added to indicate that patients in the Single-Agent Arm may be replaced if they are withdrawn from treatment before completing per-protocol pharmacokinetic (PK) assessments in the PK Run-In period. Lastly, a guide for managing patients with noninfectious pneumonitis has been added.

Purposes for Amendment 1

The purposes of this amendment are to:

- Delete the requirement to perform multiple gated acquisition scan (MUGA) or echocardiogram on Cycle 1, Day 1 and Cycle 2, Day 1.
- Add the requirement to perform fasting lipid profiles on Cycle 1, Day 1 and Cycle 2, Day 1.
- Clarify that hematology, chemistry, and urinalysis may be performed up to 24 hours before study visit on Day 1 of Cycle 3 and beyond.
- Clarify that a predose blood sample for PK analysis is required on Visit 5 during the PK Run-In period for patients in the Single-Agent Arm.
- Clarify that blood samples for [redacted]
- Clarify the patients in the Combination Arm may be administered paclitaxel beyond Cycle 6, Day 15 at the discretion of the investigator.
- Consolidate and clarify the exclusion criteria for patients with cardiovascular and pulmonary disease
- Clarify that patients taking low-dose glucocorticoids for replacement therapy may be enrolled into the study.
- Clarify that if emesis occurs after study medication administration, the dose will be counted as missed and will not be re-administered.
- Clarify that patients who experience an adverse event (AE) that meets the definition of a dose-limiting toxicity (DLT) may continue study treatment with MLN0128 up to a 33% dose reduction after the event resolves to Grade 1 or baseline values within 2 weeks of interrupting planned therapy.
- Clarify that 16 patients will complete the protocol-specified PK evaluations in the Single-Agent Arm.
- Clarify that patients in the Single-Agent Arm who are withdrawn from treatment before completing per-protocol PK assessments in the PK Run-In period will be replaced.

- Provide guidance for the management of patients with noninfectious pneumonitis.
- Update the vendor and contact information for reporting product complaints.
- Correct typographical errors, punctuation, grammar, and formatting.

14.6 Amendment 2 Rationale and Purposes

Rationale for Amendment 2

Clinical Study Protocol MLN0128-1004 was amended to evaluate the safety, tolerability, and pharmacokinetics (PK) of MLN0128 capsules based on milled active pharmaceutical ingredient (API) when administered once weekly (QW). In addition, clarifications on procedures outlined in the protocol were provided.

Purposes for Amendment 2

The purposes of this amendment were to:

Study Procedures

- Add a third arm to assess the safety, tolerability, and PK of milled MLN0128 API capsules administered QW.
- Add 1 study center and 12 to 24 patients to be enrolled into the study.
- Add the Single-Agent QW Arm to the Single-Agent QD (daily dosing) Arm Schedule of Events.
- Add blood sampling for PK analysis in the Single-Agent QW Arm.
- Clarify that 12-lead electrocardiograms (ECGs) should be performed both predose and 2 hours postdose during the Study Treatment period for patients in both the Single-Agent QD Arm and the Combination Arm.
- Clarify that bone scans may be performed to assess bony lesions in patients rather than computed tomography (CT) or magnetic resonance imaging (MRI).
- Clarify that patients in the Single-Agent QD Arm are required to fast overnight on the evenings before Visit 1 and Visit 5 of the PK Run-In Period.
- Clarify that the high-fat breakfast must be completed within 30 minutes (+5 min) followed by administration of MLN0128 within 5 minutes after completion of the high-fat breakfast on Visit 3 of the PK Run-In Period for patients in the Single-Agent QD Arm.
- Provide the fasting requirements for fasting lipid testing.
- Clarify that the blood sample to [redacted].
- Remove the requirement to measure patient weight on Day 8 in all cycles of all treatment arms.

Analysis

- Add a secondary endpoint: the PK parameters of a single dose of MLN0128 milled API capsules administered on an empty stomach in the Single-Agent QW Arm.
- Provide sample-size assumptions for the Single-Agent QW and Combination Arms.
- Clarify that single-dose PK parameters will be summarized by treatment arm as appropriate.

Eligibility

- Clarify that patients may not take strong CYP3A4, CYP2C9, or CYP2C19 inhibitors or clinically significant inducers of CYPs 3A4, 2C9, or 2C19 within 7 days of the first dose of MLN0128.
- Clarify that patients who have enteric stomata should be excluded from the study.
- Clarify that patients in the Single-Agent QD Arm participating in the PK Run-In period may not take proton pump inhibitors (PPIs) less than 5 days before the first MLN0128 PK Run-In dose or H_2 receptor antagonists within 24 hours of the first PK Run-In dose.
- Clarify that if male patients do not practice true abstinence, they must agree to practice effective barrier contraception during the entire Study Treatment period and through 120 days after the last dose of study drug.

Study Drug

- Update dose-limiting toxicity (DLT) definitions for patients in the Single-Agent QW Arm.
- Provide the dose escalation plan for the Single-Agent QW Arm.
- Provide dose modification criteria for the Single-Agent QW Arm.
- Clarify that patients who are withdrawn from treatment in Cycle 1 for reasons other than DLT will be replaced.
- Clarify that strong CYP3A4, CYP2C9, and CYP2C19 inhibitors and clinically significant enzyme inducers should only be administered with extreme caution at the discretion of the investigator.
- Clarify that patients in the Single-Agent QW Arm may take a forgotten or missed dose of MLN0128 within 12 hours of the scheduled dosing time.
- Clarify that the decision to escalate or de-escalate the dose of MLN0128 in the Combination Arm will be based on safety and review of PK data.
- Clarify that anti-emetic drugs associated with a significant risk for QT prolongation are prohibited during the study.
- Clarify that during the Study Treatment period, H_2 receptor antagonists may be allowed, if needed, provided that the histamine H_2 receptor antagonist is not taken within 12 hours before and within 6 hours after study drug administration.
- Provide clarification on guidance of the management of Grade ≥ 3 rash.
- Clarify that DLTs are defined according to the adverse event (AE) profile observed in Cycle 1 and the PK Run-In period.

Background Information

- Provide rationale for inclusion of the Single-Agent QW Arm.

14.7 Amendment 3 Detailed Summary of Changes

The primary sections of the protocol affected by the changes in Amendment 3 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.

The primary change occurs in Section 5.2 Exclusion Criteria #15:

Deleted text:	~~15. Use of strong CYP3A4, CYP2C9, or CYP2C19 inhibitors or clinically significant inducers of CYPs 3A4, 2C9, or 2C19 within 7 days of the first dose of MLN0128 (See Section 14.4 for a list of these drugs).~~

Rationale for Change:

This change, which removes enrollment restrictions for patients taking CYP3A4, CYP2C9, or CYP2C19 inhibitors and/or inducers in this study, was made to allow more flexibility in patient enrollment based on updated data on MLN0128 metabolism by specific CYP isoforms.

Change 2: Update the list of concomitant medications prohibited during the study.

The primary change occurs in Section 6.7 Excluded Concomitant Medications, Foods, and Procedures:

Initial wording:	• Strong CYP3A4, CYP2C9, and CYP2C19 inhibitors and clinically significant enzyme inducers may not be used during the PK Run-In Period or at any time during Cycle 1 (see the nonexhaustive list provided in Section 14.4). After Cycle 1, treatment with any of these medications may only be administered on a case-by-case basis after approval by the study clinician. In addition, patients should not consume food or beverages containing the fruit or juices listed in Section 14.4 within 1 week before the first dose of MLN0128 and throughout the study. […] • […]Examples of H_2 receptor antagonists include ranitidine, famotidine, cimetidine and nizatidine.

Amended or new wording:	• Strong ~~CYP3A4, CYP2C9, and CYP2C19~~ **CYP1A2** inhibitors and ~~clinically significant enzyme~~ **CYP** inducers ~~may not be used during the PK Run-In Period or at any time during Cycle 1 (see the nonexhaustive list provided in Section 14.4). After Cycle 1, treatment with any of these medications may only be administered on a case-by-case basis after approval by the study clinician.~~ **should be administered with caution and at the discretion of the investigator (refer to Section 14.4 for a list of these agents). Alternative treatments, if available, should be considered.** **[….]** • […]Examples of H_2 receptor antagonists include ranitidine, famotidine, ~~cimetidine,~~ and nizatidine. **However, cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first-choice H2 receptor antagonist (refer to Section 14.4).**

Rationale for Change:

This change was made to update the recommendations on concomitant medication use during the study based on MLN0128 metabolism by specific CYP isoforms.

Change 3 Update the list of relevant CYP inhibitors and inducers.

The primary change occurs in Section 14.4 List of Relevant Cytochrome P450 Inhibitors and Clinically Significant Enzyme Inducers:

Description of the change:	The list of relevant CYP inhibitors and inducers was updated to remove sections listing strong CYP2C19 inhibitors and strong CYP3A4 inhibitors; to add a section listing strong and moderate CYP1A2 inhibitors; and update the section listing clinically significant enzyme inducers.

Rationale for Change:
This change was made for consistency with updated data on MLN0128 metabolism by specific CYP isoforms.

Change 4 Remove dietary restrictions related to CYP inhibitors and inducers.

The primary change occurs in Section 6.7 Excluded Concomitant Medications, Foods, and Procedures:

Deleted text:	[…]~~In addition, patients should not consume food or beverages containing the fruit or juices listed in Section 14.4 within 1 week before the first dose of MLN0128 and throughout the study.~~

Rationale for Change:

The change was made for consistency with new data that removes the necessity for restrictions concerning CYP2C9 and 2C19.

The following sections also contain this change:

- Section 6.9 Precautions and Restrictions
- Section 14.4 List of Relevant Cytochrome P450 Inhibitors and Clinically Significant Enzyme Inducers.

Change 5: Insert language to reduce the required frequency of radiographic disease assessments for patients who have received at least 1 year of continuous MLN0128 treatment per protocol.

The primary change occurs in footnote "i" the Single-Agent QD and Single-Agent QW Arms Schedule of Events:

Added text:	**For long term patients, defined as study participation (greater than or equal to) 1 year, a CT (with contrast)/MRI of chest, abdomen, and pelvis will be obtained at intervals of up to every 4 cycles (plus or minus 7 days) as clinically indicated.**

Rationale for Change:

This change was made to reduce the burden and minimize radiation exposure for long-term patients.

A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	13-Dec-2017 20:47 UTC