Title: Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies

NCT Number: NCT01899053

Protocol Approve Date: 28 November 2017

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CLINICAL STUDY PROTOCOL C32001 AMENDMENT 6

MLN0128 in Combination With MLN1117

A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies

Protocol Number:	C32001
Indication:	Advanced nonhematologic malignancies
Phase:	1b
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2013-000466-11
Therapeutic Area:	Oncology

Protocol History

Original	07 March 2013
Amendment 1	29 April 2013
Amendment 2	21 January 2014
Amendment 3	05 March 2014
Amendment 4	02 April 2014
Amendment 5	25 May 2016
Amendment 6	28 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.

Protected Personal Data

Rationale for Amendment 6

This document describes the changes in reference to the protocol incorporating Amendment 6. 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, description of potential drug-drug interactions, and dietary restrictions related to CYP inhibitors and inducers have been updated accordingly. The number of required radiographic disease assessments for patients who have received at least 1 year of continuous treatment has also been modified.

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 Section 14.11.

Changes in Amendment 6

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. Update the description of potential drug-drug interactions.
5. Remove dietary restrictions related to CYP inhibitors and inducers.
6. 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 Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies

Number of Patients: Approximately 101 patients total: approximately 81 evaluable patients will be enrolled in the dose escalation stage (Escalation Stage), and approximately 20 evaluable patients will be enrolled in the Expansion Stage.

Study Objectives

Primary

- To evaluate the safety profile and to determine the dose-limiting toxicities, maximum tolerated doses (MTDs) and/or recommended phase 2 doses (RP2Ds), and dosing schedules of oral MLN0128 in combination with MLN1117 (MLN0128 + MLN1117) in patients with advanced nonhematologic malignancies
- To characterize the single- and multiple-dose plasma pharmacokinetics (PK) of MLN0128 + MLN1117 in patients with advanced nonhematologic malignancies

Secondary

- To evaluate evidence of antitumor activity of MLN0128 + MLN1117

Exploratory

- Company Confidential Information
- [redacted]
- [redacted]

Overview of Study Design

This study is a multicenter, open-label, phase 1b trial of MLN0128 (an oral mechanistic target of rapamycin complex 1/2 [mTORC1/2] inhibitor) in combination with MLN1117 (an oral inhibitor of the PI3Kα isoform) when administered to 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 2 stages: an Escalation Stage followed by an Expansion Stage. In the Escalation Stage, 2 dosing regimens for the combination will be evaluated in separate treatment arms. Throughout this protocol, "study drug" or "MLN0128 + MLN1117" refers to combination dosing of MLN0128 + MLN1117.

In the Escalation Stage, patients will be enrolled into dose escalation cohorts at different combination doses and schedules of MLN0128 and MLN1117 using a standard 3 + 3 approach to determine the

MTDs and/or RP2Ds in each treatment arm and optimal dosing schedules to be implemented in the Expansion Stage. Study drug will be administered in 28-day cycles. In Treatment Arm A, MLN0128 will be administered once daily every day (QD) and MLN1117 will be administered once daily on Monday, Wednesday, and Friday of each week. In Treatment Arm B and Arm C, both MLN0128 and MLN1117 will be administered QD on Monday, Tuesday, and Wednesday of each week.

Patients will be enrolled in the Expansion Stage to further characterize the safety, tolerability, and PK of MLN0128 in combination with MLN1117. A combination dose and schedule from 1 of the treatment arms evaluated in the Escalation Stage will be chosen to examine the mutual drug-drug interaction PK of MLN0128 and MLN1117; the dose and schedule to be examined during the Expansion Stage will be specified prior to patient enrollment into that stage.

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. Adverse events will be assessed, and laboratory values, vital signs, physical exam findings, and electrocardiograms will be obtained to evaluate the safety and tolerability of MLN0128 + MLN1117.

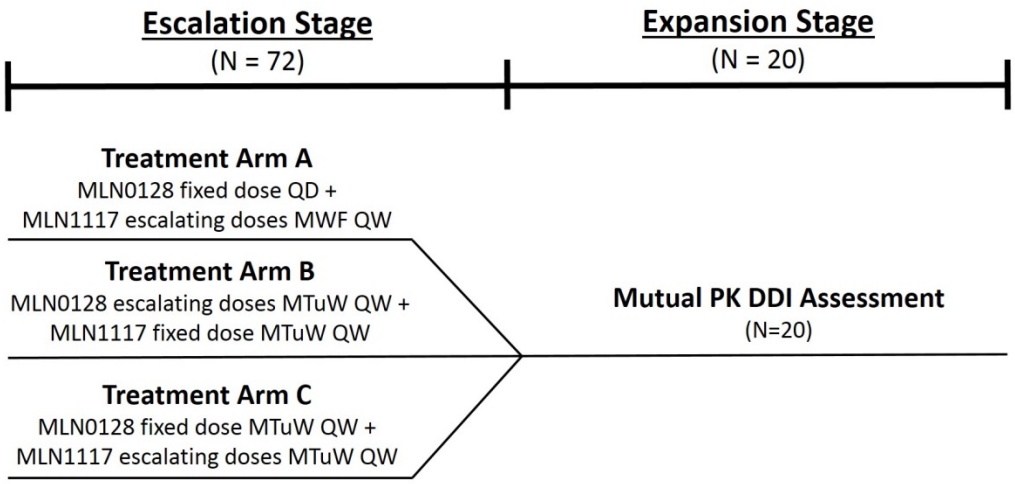
Company Confidential Information

Study Population: Adult patients (≥ 18 years old) with advanced nonhematologic malignancies. In each stage, the study population will comprise patients with any advanced nonhematologic tumor, except primary brain tumor, who satisfy all of the study inclusion/exclusion criteria.

Patients enrolled in this study will not be required to have measureable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1), but, if feasible, response may be evaluated using RECIST guidelines.

Duration of Study: The maximum duration of on-study treatment for individual patients will be 12 months. Further treatment with MLN0128 + MLN1117, if beneficial for the patient, may be permitted upon discussion with the sponsor. It is anticipated that the overall conduct of this study will last for approximately 40 months.

Figure 1-1 Study Overview Diagram



Escalation Stage

- 3+3 dose escalation
- Dose escalation will begin in Treatment Arms A and B in parallel; Arm C will initiate after confirmation of safety and tolerability in Arm B.
- Assessments include safety, MTD (for each treatment arm), DLTs, and skin pharmacodynamics.

Expansion Stage

- This stage will implement a combination dose and schedule from 1 of the treatment arms evaluated in the Escalation Stage.

RP2D and Dosing Schedule

- These will be selected for MLN0128 and MLN1117 based on safety, tolerability, pharmacodynamics, and early signs of efficacy.

Abbreviations: DDI = drug-drug interaction; DLT = dose-limiting toxicity; MTuW = Monday, Tuesday, Wednesday (dosing schedule); MWF = Monday, Wednesday, Friday (dosing schedule); MTD = maximum tolerated dose; PK = pharmacokinetics; QD = once daily every day; QW = once weekly; RP2D = recommended phase 2 dose.

SCHEDULE OF EVENTS

	Screening[a]	TREATMENT CYCLES															
		Cycle 1[b]								Cycle 2[b]				Cycles 3 and 4[b]		Cycle 5[b] plus	EOS[c]
	Within 28 days	Day 1 Predose[a]	Day 1	Day 2 (or 3[y])	Day 8	Day 15	Day 22	Day 24	Day 25	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	
Study Procedures																	
Informed Consent[d]	X																
Inclusion/Exclusion Criteria	X																
Demographics	X																
Medical History	X																
Physical Examination	X	X			X	X	X			X		X		X	X	X	X
Height	X																
Weight	X	X								X				X		X	X
Vital Signs[e]	X	X			X	X	X			X	X	X	X	X	X	X	X
ECOG Performance Status	X	X			X	X	X			X		X		X	X	X	X
Patient Diary Review		X			X	X	X			X	X	X	X	X	X	X	X
ECHO/MUGA	X																
12-lead ECG[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]			X[f]	X[f]	X[f]					X[f]
Concomitant Medications and Procedures[g]			Recorded from the first dose through 30 days after the last dose														
SAE Collection[h]	Recorded from the time the Informed Consent form is signed through 30 days after the last dose of study drug																
AE Collection			Recorded from the first dose through 30 days after the last dose														

	Screening[a]	TREATMENT CYCLES																EOS[c]
		Cycle 1[b]								Cycle 2[b]				Cycles 3 and 4[b]		Cycle 5[b] plus		
	Within 28 days	Day 1 Predose[a]	Day 1	Day 2 (or 3[y])	Day 8	Day 15	Day 22	Day 24	Day 25	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
Samples and Laboratory Assessments																		
Pregnancy Test[i]	X	X																
Urinalysis[j]	X	X				X				X		X		X	X	X	X	
Coagulation[k]	X[l]							X[l]		X		X		X		X	X	
Hematology[l]	X	X			X	X	X			X	X	X	X	X	X	X	X	
Chemistry[l]	X	X		X[w]	X	X	X			X	X	X	X	X	X	X	X	
HbA1c[x]		X[x]												X[x]		X[x]		
Fasting Glucose[m]	X[m]	X[m]	X[m]	X[m,w]	X[m]	X[m]	X[m]			X[m]		X[m]		X[m]	X[m]	X[m]	X[m]	
Fasting Insulin and Insulin C-Peptide Level[n] – ***Escalation Stage Only***	X[n]	X[n]	X[n]	X[n]	X[n]					X[n]				X[n]		X[n]	X[n]	
Fasting Lipid Profile[o]	X									X				X		X	X	
In-Home Daily Fasting Glucose Monitoring[p]				X[p,w]	X[p]	X[p]	X[p]			X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	
Blood Samples for PK[q]		See Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage), Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A), and Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C). Schedules are specific to study stage and treatment arm.																
Blood Sample for Evaluation of Germline Polymorphisms	X																	

	Screening[a]	TREATMENT CYCLES															EOS[c]
		Cycle 1[b]								Cycle 2[b]				Cycles 3 and 4[b]		Cycle 5[b] plus	
	Within 28 days	Day 1 Predose[a]	Day 1	Day 2 (or 3[y])	Day 8	Day 15	Day 22	Day 24	Day 25	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	
Urine PK[r] - ***Expansion Stage Only***		See Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A) and Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C). Schedules are specific to the treatment arm schedule implemented in the Expansion Stage.															
Tumor Tissue (banked) or Fresh Biopsy Sample[s] – ***Escalation Stage Only***	X																
Skin Biopsy[t] – ***Escalation Stage Only***	X							X	X								
Response Assessments																	
Disease Evaluation by RECIST 1.1 (CT/MRI)[u]	X												X		X	X	
Dosing																	
Treatment Arm A[v] ***Escalation Stage***			***MLN0128*** is dosed once daily every day; ***MLN1117*** is dosed once daily on MWF of each week.														
Treatment Arm B and C[v] ***Escalation Stage***			***MLN0128*** and ***MLN1117*** are both dosed once daily on MTuW of each week.														
Treatment Arm A[v] ***Expansion Stage***			***MLN0128*** is dosed once daily every day except on Day 13 through Day 19, when dose is withheld; ***MLN1117*** is dosed once daily on MWF except on Day 1 through Day 5 when dose is withheld.[v]							***MLN0128*** is dosed once daily every day; ***MLN1117*** is dosed once daily on MWF of each week.							

	Screening[a]	TREATMENT CYCLES															EOS[c]
		Cycle 1[b]								Cycle 2[b]				Cycles 3 and 4[b]		Cycle 5[b] plus	
	Within 28 days	Day 1 Predose[a]	Day 1	Day 2 (or 3[v])	Day 8	Day 15	Day 22	Day 24	Day 25	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	
Treatment Arm B and C[v] ***Expansion Stage***			***MLN0128*** is dosed once daily on MTuW of each week except on Days 15, 16, 17 when dose is withheld; ***MLN1117*** is dosed once daily on MTuW of each week except on Days 1, 2, 3 when dose is withheld.[v]							***MLN0128*** and ***MLN1117*** are both dosed once daily on MTuW of each week.							

Abbreviations: AE = adverse event; CA-125 = cancer antigen 125; CXDY = Cycle X Day Y; CT = computed tomography; DDI = drug-drug interaction; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOS = End of Study; h = hour(s); HbA1c = glycosylated hemoglobin; MRI = magnetic resonance imaging; MTuW = Monday, Tuesday, Wednesday; MUGA = multiple gated acquisition [scan]; MWF = Monday, Wednesday, Friday; PE = physical exam; PK = pharmacokinetic(s); PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a Screening assessments are performed within 28 days before the C1D1 dose. Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

b Laboratory assessments can be conducted ± 3 days of the scheduled visit, with the exception of PK/pharmacodynamic assessments or unless otherwise noted.

c The EOS visit will occur within 30 (+10) days after the last dose of study drug or before the start of subsequent antineoplastic therapy.

d Informed consent may be captured before the screening period (28 days before C1D1 dosing).

e Vital signs include blood pressure, heart rate, and temperature.

f During the Escalation Stage, single 12-lead ECGs will be conducted at the following times: screening; C1D1 predose, 2 h (± 30 min) postdose, and 4 h (± 30 min) postdose; C1D2 predose (approximately 24 h [± 2 h] after the C1D1 dose); C1D8 and C1D15 at 2 h (± 30 min) postdose; C1D22 predose; C2D1 predose and 2 h (± 30 min) postdose; C2D8 and C2D15 at 2 h (± 30 min) postdose; and the EOS visit. During the Expansion Stage, single 12-lead ECGs will be conducted at the following times: screening; C1D1 predose and 2 h (± 30 min) postdose; C1D8 and C1D15 at 2 h (± 30 min) postdose; C1D22 predose; C2D1 predose and 2 h (± 30 min) postdose; C2D8 and C2D15 at 2 h (± 30 min) postdose; and the EOS visit. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, then the ECG will be completed before the collection of the blood sample.

g See Section 6.7 for medications and procedures that are prohibited during the study, Section 6.8 for medications that should be used cautiously during the study, and Section 6.7 for restrictions on antacids and calcium supplements.

h Only those SAEs that occur after the first dose of study drug will be collected in the eCRF; however, all SAEs occurring after consent will be reported. See Sections 9.1.1, 9.1.3, 9.2, and 9.3.

i A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on C1D1 with negative results available before the first dose may be administered. A serum pregnancy test may also be performed within 3 days of dosing in place of the

	Screening[a]	TREATMENT CYCLES															EOS[c]
		Cycle 1[b]								Cycle 2[b]				Cycles 3 and 4[b]		Cycle 5[b] plus	
	Within 28 days	Day 1 Predose[a]	Day 1	Day 2 (or 3[y])	Day 8	Day 15	Day 22	Day 24	Day 25	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	

C1D1 urine test.

j See Section 7.4.14 for urinalysis panel.

k On days where tumor or skin biopsy is required, coagulation sample is required within 24 h before obtaining any skin or tumor biopsy. See Section 7.4.14 for full coagulation panel.

l Samples may be collected ± 3 days of the scheduled visit. See Section 7.4.14 for the full Hematology and Chemistry Panel.

m During the Escalation Stage, fasting glucose will be measured at the following times: screening, C1D1 predose and at 0.5 h (± 15 min), 1 h (± 15 min), and 2 h (± 30 min) after dosing; C1D2 predose; C1D8 predose and 2 h (± 30 min) postdose; C1D15 and C1D22 predose only; Cycles 2 through 4 predose on Days 1 and 15; C5D1 predose; and predose on Day 1 of every cycle thereafter; and the EOS visit. During the Expansion Stage, fasting glucose will be measured at the following times: screening; C1D1 predose; C1D3 predose; C1D8 predose and 2 h (± 30 min) postdose; C1D15 and C1D22 predose only; Cycles 2 through 4 predose on Days 1 and 15; C5D1 predose; and predose on Day 1 of every cycle thereafter; and the EOS visit. During the Expansion Stage, fasting glucose assessment on C1D1 will be done predose only.

n For patients in the Escalation Stage only, fasting insulin and insulin c-peptide will be measured at screening, C1D1 predose and 0.5 h (± 15 min), 1 h (± 15 min), 2 h (± 30 min), 4 h (± 30 min), and 8 h (± 30 min) postdose (Note that the 4 h and 8 h samples are not fasting); C1D2 at 24 ± 2 h post-C1D1 dose; C1D8 predose; C2D1 predose; predose on Day 1 of every cycle thereafter; and the EOS visit. No fasting insulin or insulin c-peptide assessments are required for patients in the Expansion Stage. See Section 7.4.14 for meal timing on C1D1.

o See Section 7.4.14 for Fasting Lipid panel.

p Patients will be given a glucometer on C1D2 (Escalation Stage) or C1D3 (Expansion Stage) to monitor daily fasting glucose levels at home and will be instructed to notify the investigator when the fasting glucose is abnormal (ie, ≥ 140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 7.4.14 for further instruction.

q Time points for blood samples for PK analysis will be collected as specified in Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage), Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A), and Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C).

r Time points for urine samples for PK analysis will be collected as specified in Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A) and Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C).

s For patients in the Escalation Stage only, tumor tissue (banked) will be required at screening as specified in Section 7.4.16. For banked tissue, the sample can be from either paraffin-embedded tumor block or unstained slides (see Section 7.4.20). If a paraffin-embedded tumor block or unstained slides are not available, the patient will be required to undergo a fresh tumor biopsy as specified in Section 7.4.16. The sample must be collected during screening before the first dose of study drug. Tumor tissue will be analyzed as described in Section 7.4.20 and will be tested retrospectively for genetic mutations. No tumor tissue is required at screening for patients in the Expansion Stage.

	Screening[a]	TREATMENT CYCLES															EOS[c]
		Cycle 1[b]								Cycle 2[b]				Cycles 3 and 4[b]		Cycle 5[b] plus	
	Within 28 days	Day 1 Predose[a]	Day 1	Day 2 (or 3[y])	Day 8	Day 15	Day 22	Day 24	Day 25	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	

t For patients in the Escalation Stage only, skin biopsies (approximately 2 mm in diameter) are to be collected according to the schedule given in the Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage). No skin biopsies are required for patients in the Expansion Stage.

u Response assessments will be performed between Days 22 to 28 of Cycle 2 and every even-numbered cycle thereafter (ie, Cycle 4, 6, etc). A CT scan with intravenous contrast of the chest, abdomen, and pelvis will be performed during screening. (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study.) If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. Prostate cancer patients should have PSA measured at screening, and PSA alone may be used for post-screening disease assessments for these patients if they lack measurable sites of disease at screening. Similarly, patients with ovarian cancer should have CA-125 measured at screening and CA-125 alone may be used. 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.

v See Section 6.1 for details on study drug dosing. MLN0128 and MLN1117 are to be taken at the same time on dosing days when both drugs are to be administered.

w For patients in the Expansion Stage, this assessment should be done on Cycle 1, Day 3.

x HbA1c testing is to be done at C1D1 and on the first day of every third cycle thereafter (eg, C4D1, C7D1, C10D1).

y Where noted in the Schedule of Events, assessments for patients enrolled in the Expansion Stage are to be collected on Day 3 instead of Day 2.

Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage)

	Screening		Cycle 1					
			Day 1	Day 2[c]	Day 24[c]		Day 25[c]	
	Fresh tumor biopsy[a]	Skin biopsy[b]	PK	PK	PK	Skin Biopsy	PK	Skin Biopsy
Anytime	X	X						
Predose (within 30 min of dosing)[c]			X	X (24 h after the Day 1 dose [± 2 h])	X		X[d] (24 h after the Day 24 dose [± 2 h])	X[d] (24 h after the Day 24 dose [± 2 h])
0.5 h (± 10 min)			X		X			
1 h (± 10 min)			X		X			
2 h (± 30 min)			X		X[d]	X (± 1 h)[d]	X[d] **Arm A only**	X (± 1 h)[d] **Arm A only**
4 h (± 30 min)			X		X			
8 h (± 45 min)			X		X[d]	X (± 1 h)[d] **Arm B and Arm C only**		

Abbreviations: aPTT = activated partial thromboplastin time; CXDY = Cycle X, Day Y; ECG = electrocardiogram; h = hour(s); min = minutes; PK = pharmacokinetic(s); PT = prothrombin time.

When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

a For patients without banked tumor tissue, a fresh tumor biopsy must be collected during screening before the first dose of study drug (before dosing on C1D1). The investigator must judge the tumor to be accessible to biopsy without crossing vital structures (eg, large blood vessels). For tumors that are not superficially accessible, biopsies will be radiographically guided (eg, by CT scanning). Patients who undergo biopsy of tumor tissue must have platelet counts ≥ 75,000/mm^3 and normal PT and aPTT (within 24 h before biopsy) and no have history of excessive bleeding nor have received antiplatelet or anticoagulant therapy in the previous 7 days (eg, clopidogrel [Plavix®] or salicylates [aspirin]) (see Section 7.4.16).

b Screening skin biopsy must be collected within 2 weeks before the first dose of study drug (before dosing on C1D1). Patients undergoing skin biopsies must have platelet counts ≥ 20,000/mm^3 and normal PT and aPTT within 24 h before the scheduled skin biopsy (see Section 7.4.16).

Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage)

	Screening		Cycle 1					
			Day 1	Day 2[c]	Day 24[c]		Day 25[c]	
	Fresh tumor biopsy[a]	Skin biopsy[b]	PK	PK	PK	Skin Biopsy	PK	Skin Biopsy

c Patients will be instructed to arrive at the clinic in the morning without taking their study drug dose(s). The timing of the visit should occur at approximately the same time as the dosing times on the previous days of the cycle.

d The plasma sample for PK analysis should be taken at the same time (± 5 min) as the skin biopsy. Patients undergoing skin biopsies must have platelet counts ≥ 20,000/mm^3 and normal PT and aPTT within 24 h before the scheduled skin biopsy (see Section 7.4.16).

Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A)

	Cycle 1								
	Day 1	Day 5[a]		Day 12[a]		Day 13[a]	Day 19[a]		Day 20[a]
	Urine PK	PK	Urine PK[c]	PK	Urine PK[c]	PK	PK	Urine PK[c]	PK
Predose (within 30 min of dosing)[a]	X[b]	X		X		X (24 h after the D12 dose [± 2 h])	X		X (24 h after the D19 dose [± 2 h])
0.5 h (± 10 min)		X	X[c] (0 – 8 h [± 1 h])	X	X[c] (0 – 8 h [± 1 h])		X	X[c] (0 – 8 h [± 1 h])	
1 h (± 10 min)		X		X			X		
2 h (± 30 min)		X		X			X		
4 h (± 30 min)		X		X			X		
8 h (± 45 min)		X		X			X		

Abbreviations: CXDY = Cycle X, Day Y; ECG = electrocardiogram; h = hour(s); min = minutes; PK = pharmacokinetic(s).

When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples.

a Patients will be instructed to arrive at the clinic in the morning without taking their study drug dose(s). The timing of the visit should occur at approximately the same time as the dosing times on the previous days of the cycle.

b A predose (blank) urine sample should be collected on C1D1 before first study drug dose administration. See the Study Manual for details on urine collection methodology.

c On Days 5, 12, and 19, patients will void the bladder immediately before study drug administration. This voided urine will not contribute to the urine PK sample collection. Urine voided subsequently during the 8 h postdose time frame will be collected for PK analysis. At the end of the sampling period, the 8 h PK sample should be collected before the patient's final urine void. See the Study Manual for details on urine collection methodology.

Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C)

	Cycle 1								
	Day 1	Day 3[a]		Day 10[a]		Day 11[a]	Day 17[a]		Day 18[a]
	Urine PK	PK	Urine PK[c]	PK	Urine PK[c]	PK	PK	Urine PK[c]	PK
Predose (within 30 min of dosing)[a]	X[b]	X		X		X (24 h after the D10 dose [± 2h])	X		X (24 h after the D17 dose [± 2h])
0.5 h (± 10 min)		X	X[c] (0 – 8 h [± 1 h])	X	X[c] (0 – 8 h [± 1 h])		X	X[c] (0 – 8 h [± 1 h])	
1 h (± 10 min)		X		X			X		
2 h (± 30 min)		X		X			X		
4 h (± 30 min)		X		X			X		
8 h (± 45 min)		X		X			X		

Abbreviations: CXDY = Cycle X, Day Y; ECG = electrocardiogram; h = hour(s); min = minutes; PK = pharmacokinetic(s).

When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples.

a Patients will be instructed to arrive at the clinic in the morning without taking their study drug dose(s). The timing of the visit should occur at approximately the same time as the dosing times on the previous days of the cycle.

b A predose (blank) urine sample should be collected on C1D1 before first study drug dose administration. See the Study Manual for details on urine collection methodology.

c On Days 3, 10, and 17, patients will void the bladder immediately before study drug administration. This voided urine will not contribute to the urine PK sample collection; however, urine voided subsequently during the 8 h postdose time frame will be collected for PK analysis. At the end of the sampling period, the 8 h PK sample should be collected before the patient's final urine void. See the Study Manual for details on urine collection methodology.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
4E-BP	4E-binding protein
AE	adverse event
AKT	protein kinase B (PKB)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration versus time curve
AUC_{24h}	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the end of the dosing interval
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
BID	twice daily
C_{max}	single-dose maximum (peak) concentration
$C_{max,ss}$	steady-state maximum peak concentration
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase 4
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
Escalation Stage	dose Escalation Stage
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Term
GI	gastrointestinal
HCSD	highest current safe dose
HER2	human epidermal growth factor receptor 2
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF1R	insulin-like growth factor 1 receptor
IRB	institutional review board
KRAS	Kirsten rat sarcoma viral oncogene homolog
LVEF	left ventricular ejection fraction
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mechanistic (formerly mammalian) target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
mTORC2	mechanistic target of rapamycin complex 2
MTuW	Monday, Tuesday, Wednesday (dosing schedule)
MUGA	multiple gated acquisition (scan)
mRNA	messenger ribonucleic acid
MWF	Monday, Wednesday, Friday (dosing schedule)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OATP	organic anion-transporting polypeptide
OCT1/2	organic cation transporter proteins 1 and 2
P-gp	P-glycoprotein
PI3K	phosphoinositol-3-kinase
PI3Kα	phosphoinositol-3-kinase alpha catalytic subunit; also p110α and PIK3CA
PIK3CA	phosphoinositol 3-kinase alpha catalytic subunit; also p110α and PI3Kα,
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PSA	prostate-specific antigen
PT	prothrombin time
PTEN	phosphatase and tensin homolog

Abbreviation	Term
QD	once daily every day
QT interval	time between the start of the Q wave and the end of the T wave on an electrocardiogram
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	once weekly; each week
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RTK	receptor tyrosine kinase
S6K	ribosomal protein S6 kinase
SAE	serious adverse event
study drug	MLN0128 in combination with MLN1117 or MLN0128 + MLN1117
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
T_{max}	single-dose time to reach maximum (peak) concentration
Treatment Arm A	once daily every day dosing for MLN0128 and once daily dosing on Monday, Wednesday, and Friday of each week for MLN1117
Treatment Arm B and Arm C	once daily dosing on Monday, Tuesday, and Wednesday of each week for both MLN0128 and MLN1117
ULN	upper limit of the normal range

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

This study will investigate the administration of MLN0128 in combination with MLN1117 in patients with advanced solid (nonhematologic) tumors. The dose escalation stage (Escalation Stage) and mutual drug-drug interaction (DDI) pharmacokinetic (PK) expansion stage (Expansion Stage) will be made up of patients with any advanced solid tumor, except primary brain tumor, who satisfy all of the study inclusion/exclusion criteria. The administration schedule and dose to be explored in the Expansion Stage will be determined prior to patient enrollment into that stage.

1.1.2 Study Drug

Throughout this protocol, "study drug" refers to combination dosing of MLN0128 + MLN1117. Properties of these 2 agents are briefly described in the following sections.

1.1.2.1 MLN0128

MLN0128, also known as TAK-228 and INK128, is an orally bioavailable, potent, and highly selective adenosine triphosphate (ATP)-competitive inhibitor of the serine/threonine kinase mechanistic (formerly mammalian) target of rapamycin (mTOR). mTOR operates in 2 distinct multi-protein complexes, mechanistic target of rapamycin complex 1 (mTORC1) and mechanistic target of rapamycin complex 2 (mTORC2), and MLN0128 inhibits both complexes. Although the component proteins of these complexes differ, both complexes contain mTOR and activate cell cycle progression.[3] mTORC1, stimulated by growth factors and amino acids, regulates cell growth by controlling the activity of ribosomal protein S6 kinase (S6K) and 4E-binding proteins (4E-BP).[4] mTORC2 regulates cell polarity and the spatial control of cell growth.[5]

Temsirolimus and everolimus, 2 mTORC1 inhibitors and analogs of rapamycin (rapalogs), were approved by the United States Food and Drug Administration (FDA). Both agents were approved for the treatment of advanced renal cell cancer. Temsirolimus was approved in 2007, and everolimus was approved in 2009 initially for the treatment of advanced renal cancer after failure of treatment with sunitinib or sorafenib.[6, 7] In addition, the FDA has recently approved everolimus in combination with exemestane for the treatment of hormone-receptor positive breast cancer.[8] Rapamycin and the other rapalogs bind to a

different site than the newly developed ATP-competitive mTOR inhibitors (such as MLN0128) and inhibit mTORC1 only. Also, of S6K and 4E-BP1, the 2 substrates phosphorylated by mTORC1, rapamycin suppresses only the phosphorylation of S6K. In contrast, MLN0128 inhibits the activities of both mTORC1 and mTORC2, including the phosphorylation of 4E-BP1 by mTORC1, and therefore, induces a significantly broader transcriptional response compared with rapamycin and the other rapalogs.[9]

1.1.2.2 MLN1117

MLN1117 is a potent and highly selective small molecule inhibitor of the class I phosphoinositol-3-kinase (PI3K) α isoform. It also equipotently inhibits activating somatic missense mutations (eg, E542K, E545K, and H1047R) in the phosphoinositol 3-kinase alpha catalytic subunit (PIK3CA) gene, encoding the p110-α catalytic subunit of PI3Kα isoform. These mutations have been identified as a major mechanism for PI3K-dependent malignant transformation, proliferation, and survival of cells. Mutations in the PIK3CA gene have been reported in various solid tumors, with the highest rates occurring in breast (27%), endometrial (24%), bladder (23%), colon (15%), and ovarian (10%) cancers.[10, 11, 12, 13] In addition, PI3Kα can be further activated by genetic mutation/amplification or activation of upstream receptor tyrosine kinases (RTKs) such as EGF receptors, human epidermal growth factor receptor 2 (HER2), insulin-like growth factor 1 receptor (IGF1R), and insulin receptors, and possibly by activated Ras. Robust antitumor activity was observed with MLN1117 in human tumor cell lines with PIK3CA mutations; clinically, partial responses have been seen in cancer patients with PIK3CA mutations treated with MLN1117.

1.2 Preclinical Experience

In compliance with the current International Conference on Harmonisation (ICH) Harmonised Tripartite Guidance S9, "Nonclinical Evaluation for Anticancer Pharmaceuticals, "(24 [ICH S9]) the nonclinical antitumor activity of MLN0128 in combination with MLN1117 has been explored in a number of experimental in vitro and in vivo tumor models. To investigate the effect of MLN0128 + MLN1117 on the downstream cellular signaling of the PI3K/protein kinase B (AKT)/mTOR pathway, Western blot analysis was performed using a diverse group of human tumor cell lines treated with MLN0128 and MLN1117 as a single agent or in combination. The treatment of MLN0128 + MLN1117 resulted in greater inhibition of these targets than either single agent. Additionally, treatment with MLN0128 + MLN1117 induced greater apoptosis, as indicated by decreased levels of total poly ADP ribose polymerase. Further, the

antiproliferative effect of MLN0128 + MLN1117 was determined against a diverse group of human tumor cell lines in vitro and in vivo. The combination exhibited at least additive activity in all other cell lines tested (HCC1419, HCC1954, MDA-MB-468, MDA-MB-436 [breast tumor], A549, NCI-H460, and NCI-H596 [lung carcinoma]). The level of inhibition observed was greater for MLN0128 + MLN1117 than either single agent alone. Antitumor activity of MLN0128 + MLN1117 was assessed in 3 xenograft models in mice: 2 breast cancer cell line models, HCC70 (triple negative breast cancer, phosphatase and tensin homolog [PTEN] null) and MDA-MB-361 (HER2-amplified breast cancer with mutated PIK3CA), and 1 colorectal cancer HCT-116 (Kirsten rat sarcoma viral oncogene homolog [KRAS] and PIK3CA mutations) models. MLN0128 and MLN1117 were administered orally as single agents or in combination concurrently using daily and intermittent schedules over 21, 28, or 30 days. The treatment of MLN0128 + MLN1117 was tolerated and resulted in a statistically significant ($p < 0.001$) increase in antitumor effects when compared with single-agent treatment in multiple treatment schedules in mice bearing HCC70 and MDA-MB-361 human breast cancer xenografts, in the latter of which substantial tumor growth delay was demonstrated. The treatment of MLN0128 + MLN1117 was also tolerated and resulted in a statistically significant ($p = 0.003$) increase in antitumor effects when compared to single-agent treatment in mice bearing HCT-116 human colorectal carcinoma xenografts.

The principal adverse effects associated with the administration of each agent are consistent with their respective mechanisms of action. Based on the available single-agent nonclinical and clinical safety data for MLN0128 or MLN1117, the expected overlapping nonclinical combination toxicities (including bone marrow and lymphoid depletion, effects on glucose/insulin homeostasis including hyperglycemia, and potential effects on chloride and cholesterol levels) can be monitored with routine clinical hematology and serum chemistry evaluations and are expected to be reversible and manageable in the clinic. Results from in vitro drug metabolism and PK studies suggest that the potential for DDIs between MLN0128 and MLN1117 in humans is low.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN0128 and of MLN1117 may be found in the respective Investigator's Brochures (IBs) for MLN0128, MLN1117, and MLN0128 + MLN1117.

1.3 Clinical Experience

Clinical experience with MLN0128, MLN1117, and MLN0128 + MLN1117 is summarized in the subsections that follow. Further details are provided in the respective IBs for MLN0128, MLN1117, and MLN0128 + MLN1117.

1.3.1 Clinical Experience With MLN0128

The clinical development program studying MLN0128 in patients with advanced solid malignancies includes 5 ongoing or completed phase 1 studies (INK128-001, INK128-003, MLN0128-1004, and C31002) and 1 ongoing phase 1b/2 study (C31001). A sixth phase 1 study in patients with multiple myeloma or Waldenström macroglobulinemia (INK128-002) has also been completed. These studies were 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 HER2-targeting agents.

1.3.1.1 Clinical PK of MLN0128

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

The PK properties of MLN0128 are detailed in the MLN0128 IB.

1.3.2 Clinical Experience With MLN1117

As of 23 June 2014, 78 patients have been enrolled into the Dose Escalation phase of Study INK1117-001 and have received at least 1 dose of MLN1117.

Patients have been treated according to 4 dosing schedules: once daily every day (QD; 24 patients) at doses ranging from 100 to 300 mg; once daily on Monday, Wednesday, and Friday of each week (MWF QW; 30 patients) at doses ranging from 200 to 1200 mg; once daily on Monday, Tuesday, and Wednesday of each week (MTuW QW; 23 patients) at doses ranging from 200 to 900 mg; and twice daily on Monday, Wednesday, and Friday of each week (BID MWF QW; 1 patient) at a dose of 300 mg.

1.3.2.1 Clinical PK of MLN1117

The preliminary PK data from patients under the QD, MTuW QW, and MWF QW dosing schedules in study INK1117-001 show that MLN1117 exhibits fast oral absorption with T_{max} occurring approximately 2 hours after dosing and a mean plasma $t_{1/2}$ of approximately 11 hours (range, 7.82 to 13.2 hours) across all cohorts. MLN1117 did not accumulate in plasma to any meaningful extent under QD dosing (accumulation ratio of approximately 1.2) in either of the intermittent dosing schedules. With the $t_{1/2}$ of approximately 11 hours and treatment-free periods for the MWF QW and MTuW QW schedules of 48 hours and 96 hours, respectively, no appreciable accumulation is expected for either the MTuW QW or MWF QW MLN1117 dosing schedules of MLN0128 + MLN1117.

Systemic exposures of MLN1117 increased with escalating doses, and there was a 9-fold increase in exposure with a 12-fold increase in dose from 100 to 1200 mg. However, a high degree of PK variability was observed across cohorts (percent coefficient of variation [CV%] values ranging from 52% to 103% for area under the plasma concentration versus time curve [AUC] from zero to 24 hours [AUC_{24h}] and 63% to 113% for area under the plasma concentration versus time curve from zero to infinity [AUC_{inf}]).

Because MLN1117 exhibits pH-dependent aqueous solubility with values of approximately 1 mg/mL at pH 1.3 and approximately 0.001 mg/mL at pH 5 and above, gastric pH-modifying agents have the potential to interfere with MLN1117 absorption. The risk for DDI therefore does exist if antacids are co-administered with MLN1117, as such agents can decrease the oral absorption and systemic exposure of MLN1117. See Section 6.7 for prohibited medications.

Details on the PK properties of MLN1117 are provided in the MLN1117 IB.

1.3.3 Clinical Experience With MLN0128 in Combination With MLN1117

This study initiated with enrollment into Treatment Arm A at 2 mg MLN0128 QD and 100 mg MLN1117 MWF QW. Dose escalation proceeded according to the 3 + 3 design dose escalation rules, outlined in Section 6.4, by 1 dose level of MLN0128 (Cohort 2A; refer to Table 6-1). Enrollment into Treatment Arm B was planned to begin, at the combination dose and schedule of 6 mg MLN0128 QD and 100 mg MLN1117 MTuW QW, after evaluation of safety in Treatment Arm A; however, dose escalation and the initiation of additional cohorts were stopped because the study drug combination of 4 mg MLN0128 and 100 mg MLN111 administered in Cohort 2A was not tolerable.

Preliminary skin pharmacodynamic data assessed from Cohorts 1A and 2A of this study suggest meaningful target inhibition of both mTORC1 and mTORC2 downstream markers.

1.4 Study Rationale

It is hypothesized that the combined inhibition of mTOR (by MLN0128) and of PI3Kα (by MLN1117) will disrupt negative-feedback signaling through AKT and thereby result in higher rates of cancer cell death and enhanced tumor control than observed with either agent alone. In a variety of different nonclinical and clinical settings, it has become clear that using targeted signal transduction monotherapy can lead to pathway reactivation by feedback mechanisms including ones targeting the PI3K/AKT/mTOR pathway.[(14)]

Although inhibition of key mediators of both mTORC1 and mTORC2 signaling by MLN0128 has demonstrated antiproliferative activity in a broad range of nonclinical cancer models, the existence of several negative feedback loops in the mTOR pathway may limit the therapeutic efficacy of MLN0128.[(15)] It has been demonstrated that inhibition of mTORC1 and mTORC2 leads to AKT (S473) dephosphorylation and a rapid but transient inhibition of AKT (T308) phosphorylation and AKT signaling. However, inhibition of mTOR also relieves feedback inhibition of RTKs, leading to subsequent PI3K activation and rephosphorylation of AKT (T308) sufficient to reactivate AKT activity.[(16)] Thus, it is hypothesized that inhibition of mTORC1/2 by MLN0128 could induce reactivation of the PI3K/AKT/mTOR pathway, thereby limiting sustained regulation of downstream effector proteins of mTOR. The addition of the PI3Kα inhibitor MLN1117 should counteract this pathway reactivation by suppressing 2 different nodes of the PI3K/AKT/mTOR pathway.

While the strategy of combining the mTORC1/2 inhibitor MLN0128 with the PI3Kα inhibitor MLN1117 could be considered analogous to the use of dual mTOR/PI3K inhibitors currently being evaluated clinically, there are several distinct and important differences. First, the relative potencies of the dual mTOR/PI3K inhibitors against mTOR and PI3K isoforms are predetermined and may not be optimal for achieving maximal anti-tumor activity and avoiding overlapping toxicities. Second, combination of MLN0128 + MLN1117 allows for the evaluation of different dosing schedules of each agent to determine the most optimal overlap in exposure of MLN0128 and MLN1117 for effective antitumor activity and safety. Early clinical data recently published on leading dual mTOR/PI3K inhibitors has shown that tolerated doses lead to only partial pathway inhibition and limited clinical benefit, suggesting the limitations of a dual mTOR/PI3K inhibitor in a single

molecule.[17] More complete suppression of the PI3K/AKT/mTOR pathway is expected by the combination of MLN0128 and MLN1117.

As described in Section 1.2, MLN0128 in combination with MLN1117 leads to additive or synergistic anti-tumor activity in a broad array of tumor types irrespective of genotype. Treatment with MLN0128 + MLN1117 also displays stronger inhibition of AKT and induces greater apoptosis in tumor cells than either agent alone. Similarly, in vivo combination studies also support these findings, as evidenced by enhanced antitumor activity and longer tumor regrowth delay in nonclinical xenograft models.

MLN0128 + MLN1117 was well-tolerated when dosed in mice with human tumor xenografts. Based on these studies and the single-agent clinical experience to date, the expected overlapping toxicities of MLN0128 + MLN1117 can be monitored and are expected to be reversible and manageable in the clinic. Furthermore, the potential for DDIs between MLN0128 and MLN1117 in humans is expected to be low.

Taken together, the addition of MLN1117 to MLN0128 is considered to be an optimal strategy to mitigate the reactivation of the PI3K/AKT/mTOR pathway with single-agent MLN0128 treatment as well as induce a more complete suppression of the PI3K/AKT/mTOR pathway.

1.4.1 Original Protocol Rationale for Dosing Schedules, Starting Doses, and Dose Escalation Design

The combination dosing schedules of MLN0128 and MLN1117 were selected on the basis of predicted safety and tolerability profiles of each agent in the single-agent studies INK128-001 (MLN0128) and INK1117-001 (MLN1117). On the basis of data from these studies, the MLN0128 QD and MLN1117 MWF QW dosing schedules allow for continuous mTORC1/2 inhibition by MLN0128 with QD dosing and concurrent inhibition of the PI3K and mTORC1/2 pathways for 3 days of the week (MWF) through the addition of MLN1117. Additionally, on the basis of data from these studies, the dosing schedule for MLN0128 and MLN1117 on MTuW QW allows for inhibition of PI3K and mTORC1/2 pathways on MTuW followed by a 4-day dosing holiday from both agents.

The initial proposed starting dose for Treatment Arm A of 2 mg MLN0128 QD was 1 dose level below the single-agent maximum tolerated dose (MTD) in Study INK128-001 (ie, 4 mg QD). This dose was considered a safe starting dose, as no dose-limiting toxicities (DLTs) were observed with this dose in study INK128-001. The initial proposed starting

dose of 100 mg MLN1117 MWF QW was 9-fold lower than the single-agent highest current safe dose (HCSD; ie, 900 mg MWF QW) in Study INK1117-001. In Study INK1117-001, dose escalation for MWF QW dosing of MLN1117 started with 200 mg; none of the 3 treated patients experienced a DLT.

The initial proposed starting dose for Treatment Arm B was to be 6 mg MLN0128 and 100 mg MLN1117, both on MTuW QW. These proposed starting doses were, for MLN0128, 66.7% of the single-agent MTD in Study INK128-001 (ie, 9 mg) and, for MLN1117, 9-fold reduction of the single-agent HCSD for MTuW QW dosing in Study INK1117-001 (ie, 900 mg).

Additionally, since no PK-based DDIs between MLN0128 and MLN1117 are expected, it was projected that the plasma exposures of the starting doses of MLN0128 and MLN1117 would be less than those at the respective single-agent exposures at the MTDs or the HCSDs in the MLN0128 QD schedule and the MLN1117 MWF QW schedule.

As shown in Table 1-1, the initially planned starting dose of 2 mg of MLN0128 and 100 mg of MLN1117 in Treatment Arm A was predicted to provide plasma AUC on dosing days below those considered bioactive in preclinical pharmacology studies conducted in tumor xenograft models and associated with stasis. For Treatment Arm B, at the combination starting dose of 6 mg MLN0128 and 100 mg MLN1117, exposures are predicted to be within the bioactive range.

Table 1-1 Predicted Plasma Exposures of MLN0128 and MLN1117 at the Starting Doses for Treatment Arm A and Arm B

Drug	Starting Dose (mg)	Projected AUC_{24h} (ng*h/ml)[a]	Bioactive AUC_{24h} or AUC range (ng*h/ml)[b]
Treatment Arm A			
MLN0128	2	~95	137-372
MLN1117	100	~23680	~50,000
Treatment Arm B			
MLN0128	6	~240	137-372
MLN1117	100	~23680	~50,000

Abbreviations: AUC = area under the plasma concentration versus time curve; AUC_{24h} = area under the plasma concentration versus time curve from time 0 to 24 h postdose; h = hour; mg = milligrams; ml = milliliters; ng = nanogram.

a AUC_{24h} on dosing days.

b Projected human bioactive AUC associated with stasis in preclinical pharmacology studies after correcting for interspecies difference in plasma protein binding.

In addition, preliminary pharmacodynamic assessments (in skin) in the single-agent studies (INK128-001 and INK1117-001) showed that neither the 2 mg dose of MLN0128, nor the 100 mg dose of MLN1117 (in the QD regimen), provide any meaningful pharmacodynamic effects in skin, as measured by inhibition of downstream markers of mTORC1 and mTORC2 (for MLN0128) and inhibition of AKT (for MLN1117). The collective data available for Protocol Amendment 1 supported the selection of the adjusted starting doses for MLN0128 in combination with MLN1117 in this study.

Dose escalation of the combination in this study began according to the 3 + 3 rules shown in Section 6.4. In each treatment arm, MLN0128 dose levels were to be escalated at fixed MLN1117 dose levels. This approach allows for the titration of MLN0128 up to a dose that is bioactive, while maintaining a low enough dose of MLN1117 to allow the safety and tolerability of the combination to be established. MLN1117 would then be titrated up to pharmacologically active levels. The serial dose escalation of each agent separately enables the determination of the minimum exposure required for effective inhibition of the mTOR/PI3K/AKT pathway that is safe and tolerable.

1.4.2 Protocol Amendment 2 Rationale for Dosing Schedules, Starting Doses, and Dose Escalation Design

As of Protocol Amendment 2, new starting combination doses are planned, the dose escalation schedule adjusted, and a third treatment arm added (Treatment Arm C) to further evaluate the combination during the Escalation Stage (refer to Table 6-1).

The starting dose of MLN0128 in Treatment Arm A will be reduced to the initial starting dose administered in this study (2 mg QD) due to DLTs. In this manner, the combination may be re-evaluated at higher dose levels of MLN1117. The starting dose of MLN1117 for Treatment Arm A is 200 mg, approximately 22% of the single-agent MTD in both the MTW QW and MWF QW dosing schedules in Study INK1117-001 (ie, 900 mg) and 1 dose level higher than the initial dose of MLN1117; however, it is still predicted to be safe, tolerable, and within the bioactive range (projected AUC_{24h} of approximately 43,000 ng*h/ml).

Treatment Arm C has been added at the same dosing schedule as Arm B (MTuW QW for both agents). The starting dose of MLN0128 for Treatment Arm B and Arm C is 3 mg MLN0128, approximately 33% of the single-agent MTD in study INK128-001 (ie, 9 mg) and 1 dose level higher than the initial dose of MLN0128; however, it is still predicted to be safe, tolerable, and within the bioactive range (projected AUC_{24h} of approximately

205-558 ng*h/ml). The starting dose of MLN1117 for Treatment Arm B is 100 mg. The starting dose for MLN1117 in Treatment Arm C is dependent on the safety and tolerability observed in Treatment Arm B.

Dose escalation will continue to proceed according to the same 3 + 3 design and dose escalation rules (refer to Section 6.4). The dose escalation plan is designed such that Treatment Arm A will evaluate increasing levels of MLN1117 in combination with fixed doses of MLN0128. Treatment Arm B will evaluate increasing levels of MLN0128 in combination with a fixed dose of MLN1117 as tolerated. Treatment Arm C will evaluate increasing levels of MLN1117 in combination with MLN0128 at a fixed dose.

Dose escalation will begin in Treatment Arm A (Cohort 3A) and Arm B (Cohort 1B) in parallel. Dose escalation in Treatment Arm C will only initiate after confirmation of the safety and tolerability of study drug administration in Cohort 2B of Treatment Arm B.

1.4.3 Rationale for PK Assessments

The rationale for the PK assessments planned for this study is given in the following section.

PK Assessments During the Escalation Stage

Serial PK sampling in the Escalation Stage will evaluate systemic exposures of MLN0128 and MLN1117 and provide data on the dose/exposure/toxicity relationship of the combination. Data will inform the selection of the recommended phase 2 doses (RP2Ds) and schedules, which will be evaluated in the Expansion Stage of the study. See Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage) in the Schedule of Events for the PK sampling scheme used in the Escalation Stage.

PK Assessments in the Expansion Stage

Patients with any advanced solid tumor and who meet all inclusion/exclusion criteria can be enrolled into the Expansion Stage. This stage will be dedicated to collecting DDI data to characterize the effect of MLN0128 on MLN1117 PK and, conversely, the effect of MLN1117 on MLN0128 PK at the RP2D. Serial PK sampling will evaluate the systemic exposures of MLN0128 and MLN1117 when the agents are administered either alone or together.

In addition, patients in the Expansion Stage will also provide urine samples on 3 separate occasions during Cycle 1 (collected as single predose voids and single cumulative 0- to 8-hour postdose duration on prespecified days during Cycle 1). Urine will be collected to

understand the extent to which MLN0128 and MLN1117 are excreted in urine (renal clearance of both agents). The collection of urine when these agents are administered alone and when these agents are co-administered will also help evaluate whether each agent affects the renal clearance of the other when co-administered.

The PK sampling schemes for the mutual DDI assessments during the Expansion Stage are provided in Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A) and Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C).

1.4.4 Rationale for Pharmacodynamic Assessments

Assessment of Biomarkers in Tumor Tissue (Banked or Pretreatment Tumor Biopsy)

Clinical response to MLN1117 has been seen in patients with PIK3CA mutations. When using in vitro proliferation as an endpoint it has been demonstrated that PTEN loss confers insensitivity to MLN1117 with concentration producing 50% inhibition (IC_{50}) values > 10 μM. However, more recently in a PTEN null human tumor breast cancer xenograft model, MLN1117 did show some tumor growth inhibition that was significantly enhanced when assessed in the combination of MLN0128 + MLN1117. Company Confidential Information

Assessment of Pharmacodynamic Markers in Skin

The evaluation of PI3K/mTOR pathway markers in both tumor and surrogate tissues in clinical studies has contributed to the identification of an optimal dosing regimen.[18] Although pharmacodynamic effects in tumor tissues are more important to estimate antitumor activities of an anticancer agent, those in surrogate tissues such as skin have been shown concordant to changes in pharmacodynamic markers in tumor tissues and can be used as supportive evidence of the inhibition of intended target(s). In both MLN0128 and MLN1117 phase 1 studies, analyses of skin biopsy samples have revealed inhibition of PI3K/mTOR pathway marker expression. Further details are in the IBs for MLN0128, MLN1117, and MLN0128 + MLN1117. Although the number of paired skin and tumor samples analyzed to date was small, concordance in pharmacodynamic effects has been seen

between skin and tumor samples collected in the MLN0128 phase 1 study (INK128-001). Thus, in addition to characterization of safety profiles and PK, all patients in the Escalation Stage will undergo skin biopsies and PI3K/mTOR pathway markers will be evaluated to support identification of a regimen of MLN0128 + MLN1117 that can produce better antitumor activity, with an acceptable toxicity profile, than either single agent alone.

Pharmacogenomic Assessments

Genetic variation has been observed in the drug metabolizing enzymes that contribute to MLN0128 and MLN1117 metabolism (eg, cytochrome P450 [CYP] 2C9 and CYP2C19). Such variations can contribute to the interindividual variability in the PK and, in turn, the safety and efficacy of MLN0128 and MLN1117. Accordingly, blood samples will be obtained from all patients at screening to allow for the evaluation of germline polymorphisms in CYP2C9 and CYP2C19 genes. See Section 7.4.19 for more details.

1.5 Potential Risks and Benefits

Across the MLN0128 + MLN1117 dose levels and schedules to be investigated in this study, the most common treatment-emergent adverse events (TEAEs) are expected to be consistent with the pharmacodynamic mechanism of mTOR inhibition that is seen with rapalogs (mTORC1 inhibition) or dual mTORC1/2 inhibitors; these TEAEs were generally manageable with supportive care, and/or interruption or dose reduction of study drug. The most commonly reported study drug-related adverse events (AEs) across the MLN0128 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, and blood creatinine increased.

Although clinical experience with MLN1117 is limited, preliminary data show that the reported AEs have been expected from the clinical profiles observed with other PI3K inhibitors. The commonly encountered class-related toxicities, including diarrhea, hyperglycemia, and rash, have been milder after MLN1117 administration compared with those reported following administration of unselective pan-PI3K inhibitors. Although most of the AEs considered by the investigator to be related to MLN1117 administration have been mild in severity and manageable with routine standard of care, Grade 2 to 3 asymptomatic aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevations have been dose-limiting when administered on a QD schedule. Upon dose interruption, these AST/ALT elevations were reversible and manageable.

To determine the potential overlapping toxicities associated with MLN0128 and MLN1117, the identified and potential risks of both drugs, including data from nonclinical and clinical studies for each product, have been reviewed. More detailed information on the identified and potential risks of both drugs is included in their individual single-agent IBs. Class effects of mTOR inhibitors (for MLN0128) and PI3K inhibitors (for MLN1117) have also been considered. Potential overlapping toxicities for both agents include:

- Dermatologic disorders (pruritus, rash)
- Gastrointestinal (GI) disorders (diarrhea, mucosal inflammation, nausea, stomatitis, vomiting)
- Generalized disorders (anorexia, asthenia, decreased appetite, fatigue)
- Hematologic disorders (lymphoid, bone marrow depletion)
- Metabolic disorders (decreased blood chloride, hypercholesterolemia, hyperglycemia)

Based on the current clinical experience and the previous list of potential overlapping toxicities, hyperglycemia, diarrhea, nausea, vomiting, fatigue, and rash are the most anticipated AEs associated with the MLN0128 + MLN1117 combination regimen. These events are expected to be manageable.

Risk mitigation strategies for potential AEs include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent clinical and laboratory results monitoring, guidelines for management of potential toxicities, criteria for dose modification, criteria for determining DLTs, and regular monitoring of AEs and serious adverse events (SAEs) by the sponsor. In addition, patients will be given a glucometer to monitor daily predose fasting glucose levels at home and will be instructed to notify the study staff when the fasting glucose is abnormal. All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff.

1.5.1 Drug-Drug Interaction Risk Assessment

1.5.1.1 Drug Interaction Risk With MLN0128

Drug Metabolism

Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that MLN0128 is metabolized primarily via CYP1A2 (approximately 31% to 40%), with a minor contribution from CYP3A4 (approximately 11% to 22%). These data suggest that MLN0128 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-uridine diphosphate glucuronosyltransferase (UGT) pathway (approximately 18%). The new data differ from the previous in-vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in MLN0128 metabolism.

In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with MLN0128 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers (see Appendix 14.4) should only be administered with caution and at the discretion of the investigator during the study**.** Alternative treatments, if available, should be considered**.**

In vitro, MLN0128 neither inhibited any of the major CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, with IC_{50} values > 25 µM) nor induced CYPs 1A2, 2B6, or 3A4/5 at concentrations less than or equal to 10 µM. The projected total plasma steady state maximum peak concentration ($C_{max,ss}$) of MLN0128 at the proposed highest QD dose of 5 mg MLN0128 (mean projected total $C_{max,ss}$ of 0.07 µM) and a QD×3d QW dose of 12 mg MLN0128 (mean projected total $C_{max,ss}$ of 0.22 µM) are substantially lower than the IC_{50} value of 25 µM for CYP inhibition and the highest tested CYP-induction concentration of 10 µM, where CYP-induction was not observed. MLN0128 is thus unlikely to precipitate a CYP inhibition- or induction-mediated interaction for substrates of these enzymes.

Drug Transporter

In vitro, MLN0128 was neither a substrate nor an inhibitor of P-glycoprotein (P-gp) but did inhibit breast cancer resistance protein (BCRP, IC_{50} approximately 51.9 µM) and organic cation transporter proteins 1 and 2 (OCT1 and OCT2, with IC_{50} values of 21.6 and 18.9 µM, respectively).

At the doses to be administered in this study, MLN0128 is unlikely to precipitate a clinically meaningful drug interaction with substrates of BCRP, OCT1, or OCT2 based on comparisons of the potencies for inhibition of these transporters to the systemic exposures of MLN0128 expected to be achieved clinically.

1.5.1.2 Drug Interaction Risk With MLN1117

Drug Metabolism

On the basis of preliminary in vitro metabolism experiments, MLN1117 is primarily metabolized by CYP3A4 (72%), with minor contributions from CYPs 1A2 (12%), 2C9 (9%), and 2C8 (6%). In vitro, MLN1117 did not inhibit any of the major CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, with IC_{50} values > 100 µM). The mean observed total plasma $C_{max,ss}$ at the highest studied QD dose of 300 mg MLN1117 is approximately 21 µM (single-agent study INK1117-001). In the current study, MLN1117 is administered at ≥ 100 mg on 2 QD×3d QW dosing schedules. Because the projected plasma concentration of MLN1117 at doses of approximately 300 mg is substantially lower than the CYP inhibition IC_{50} of 100 µM in either QD×3d QW dosing schedule, the risk of a CYP inhibition-mediated DDI with MLN1117 is considered to be low.

In vitro CYP-induction experiments evaluating CYPs 1A2, 2B6, and 3A4/5 have shown that MLN1117 increases CYP messenger ribonucleic acid (mRNA) expression (generally < 2-fold and 20% of positive controls, omeprazole, phenobarbital, and rifampin, respectively, for CYPs 1A2, 2B6, and 3A4/5) but not CYP activity at concentrations ≤ 30 µM MLN1117. Hepatocyte preparation from 1 donor showed increased CYP3A mRNA expression > 20% (approximately 42.2%) of that of positive-control rifampin but no increase in CYP3A activity. Rather, there was a slight decrease (approximately 16%) in CYP activity at a concentration of 30 µM MLN1117. These data suggest that at doses up to 30 µM, MLN1117 does not increase CYP1A2, 2B6, or 3A4/5 activity. Based on available information and understanding of MLN1117 PK, it is also unlikely that free plasma $C_{max,ss}$ > 30 µM would be expected in either of the 2 dosing schedules, even at a dose of 400 mg of MLN1117. Thus, although a risk for CYP induction-mediated DDI cannot be excluded, there appears to be a low likelihood that MLN1117 would precipitate a CYP induction-mediated DDI at the doses planned for this study. Based upon the preliminary metabolism data for MLN1117, the cautious use of strong CYP1A2 inhibitors is allowed only at the discretion of the investigator during the study (see Appendix 14.4).

Drug Transporter

In vitro, MLN1117 was neither a substrate nor an inhibitor of P-gp. However, MLN1117 did inhibit BCRP (IC_{50} of 29.9 μM), OCT1 (IC_{50} of 2.3 μM), and OCT2 (IC_{50} of 5.8 μM) in vitro. Because the projected plasma concentrations of MLN1117 at doses > 200 mg do meet the criteria defined by the FDA in the draft DDI guidance (estimated accumulation ratio > 1.25, based on total plasma $C_{max,ss}$ of MLN1117, for transporters such as BCRP and OCT1, and ratio of free $C_{max,ss}/IC_{50}$ being > 0.1 for transporters such as OCT2), there is a potential for MLN1117 to affect the PK of BCRP substrates (eg, methotrexate, imatinib, topotecan, lapatinib, rosuvastatin) as well as OCT1 or OCT2 substrates (eg, metformin, cimetidine, amantadine, famotidine, pindolol). Thus, if patients require treatment with medications that are known substrates of these transporters, these agents should be administered with caution or alternate treatment options should be considered. It is recommended that patients requiring metformin for hyperglycemia resulting from MLN0128 + MLN1117 administration begin treatment with the lowest effective dose of metformin and have glycemic levels closely monitored.

Physicochemical

MLN1117 exhibits pH-dependent aqueous solubility (solubility is approximately 1 mg/mL at pH = 1.3 and 0.001 mg/mL at pH ≥ 5). Therefore, there exists a risk for a DDI as a result of concomitant administration with gastric pH-altering agents (eg, proton pump inhibitors [PPIs], H_2-receptor antagonists, or neutralizing antacids). Such agents are prohibited from being co-administered with MLN1117, because they could significantly decrease the oral absorption and hence the systemic exposure of MLN1117.

1.5.1.3 Drug Interaction Risk Between MLN0128 and MLN1117

Based on the available in vitro data, projected exposures, and clinically relevant dose ranges for each agent, the likelihood of meaningful drug metabolism or transporter mediated DDI between these agents is considered low. Following the determination of the RP2Ds and schedules of MLN0128 + MLN1117 in the Escalation Stage, the PK of MLN0128 and MLN1117 administered in combination will be evaluated in reference to the PK of MLN0128 and MLN1117 administered alone in the Expansion Stage. This stage will permit a formal estimation of the magnitude of mutual DDI between the 2 agents, which will support future clinical development of the combination at the RP2D determined in this study.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are as follows:

- To evaluate the safety profile and to determine DLTs, MTDs and/or RP2Ds, and dosing schedules of oral MLN0128 + MLN1117 in patients with advanced nonhematologic malignancies
- To characterize the single- and multiple-dose plasma PK of MLN0128 + MLN1117 in patients with advanced nonhematologic malignancies

2.2 Secondary Objectives

The secondary objective is as follows:

- To evaluate evidence of antitumor activity of MLN0128 + MLN1117

2.3 Exploratory Objectives

The exploratory objectives are as follows:

- Company Confidential Information
-
-

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints are as follows:

- AEs, SAEs, assessments of clinical laboratory values, physical exam findings, electrocardiograms (ECGs), and vital sign measurements
- MLN0128 and MLN1117 plasma PK parameters including, but not limited to, single-dose maximum (peak) concentration (C_{max}), T_{max}, area under the concentration-time curve from time 0 to the end of the dosing interval (AUC_{last}), $t_{1/2}$, apparent oral clearance, peak-to-trough ratio, and accumulation ratio

3.2 Secondary Endpoints

The secondary endpoint is as follows:

- Measures of disease response including objective response rate and duration of response, based on investigator's assessment and using, if feasible, the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1)

3.3 Exploratory Endpoints

The exploratory endpoints are as follows:

- Company Confidential Information
- [redacted]
- [redacted]
- [redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This study is a multicenter, open-label, phase 1b trial of MLN0128 (an oral mTORC1/2 inhibitor) in combination with MLN1117 (an oral inhibitor of the PI3Kα isoform) when administered to 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 2 stages: a (dose) Escalation Stage followed by an Expansion Stage. In the Escalation Stage, 2 dosing regimens for the combination will be evaluated in 3 separate treatment arms to identify the MTDs and/or RP2Ds and schedules to be implemented in the Expansion Stage. Throughout this protocol, "study drug" or "MLN0128 + MLN1117" refers to MLN0128 in combination with MLN1117.

In the Escalation Stage, patients will be enrolled into dose escalation cohorts at different combination doses and schedules of MLN0128 and MLN1117 using a standard 3 + 3 approach to determine the MTDs and/or RP2Ds in each treatment arm and optimal dosing schedules to be implemented in the Expansion Stage. Study drug will be administered in 28-day cycles. In Treatment Arm A, MLN0128 will be administered QD and MLN1117 will be administered once daily on MWF QW. In Treatment Arm B and Arm C, both MLN0128 and MLN1117 will be administered on MTuW QW. MLN1117 dose levels will be escalated in combination with fixed doses of MLN0128 in Treatment Arm A and Arm C; the MLN0128 dose level will be escalated in combination with a fixed dose of MLN1117 in Treatment Arm B.

Patients will be enrolled in the Expansion Stage to further characterize the safety, tolerability, and PK of MLN0128 in combination with MLN1117. A combination dose and schedule from 1 of the treatment arms evaluated in the Escalation Stage will be chosen to examine the mutual DDI PK of MLN0128 and MLN1117; the dose and schedule to be examined during the Expansion Stage will be specified prior to patient enrollment in that stage.

Patients enrolled in this study will not be required to have measureable disease per RECIST criteria (Version 1.1); however, if feasible, response may be evaluated using RECIST guidelines.[(2)]

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.[(1)]

DLTs are defined in Section 6.3. AEs will be assessed, and laboratory values, vital signs, physical exam findings, and ECGs will be obtained to evaluate the safety and tolerability of MLN0128 + MLN1117.

[redacted]

4.2 Number of Patients

Approximately 101 evaluable patients total will be enrolled in this study from approximately 12 study centers located in North America and Europe. Approximately 81 evaluable patients will be enrolled in the Escalation Stage, and approximately 20 evaluable patients will be enrolled in the Expansion Stage.

A patient will be considered enrolled at the time of administration of the first study drug dose.

4.3 Duration of Study

Patients, including those who achieve a clinical response, may receive study drug until they experience disease progression. Patients will discontinue treatment if they have an unacceptable drug-related toxicity. The maximum duration of treatment, however, will be 12 months unless it is determined that a patient would benefit from continued therapy beyond 12 months.

Patients will be followed for 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, to permit the detection of any delayed treatment-related AEs.

It is anticipated that the overall conduct of this study will last for approximately 40 months.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Patients must have a diagnosis and documented disease progression of a solid tumor malignancy, excluding primary brain tumor, for which standard, curative, or life-prolonging treatment does not exist or is no longer effective. Patients with locally advanced or metastatic solid tumors who have a history of brain metastasis are eligible for the study as long as their brain metastases have been treated and there is no evidence of progression or hemorrhage after treatment; they have discontinued dexamethasone for 4 weeks before first administration of study drug; and they have no ongoing requirement for dexamethasone or anti-epileptic drugs.

3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (see Section 14.2).

4. 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 (ICF) 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 subject. (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 postvasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

5. Voluntary written consent must be given 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.

6. Suitable venous access for the study-required blood sampling, including PK and pharmacodynamic sampling.

7. In the Escalation Stage only, patients must have a block of banked tumor tissue and/or fresh tumor tissue or at least 10 unstained slides available to be sent to the central laboratory. A patient who satisfies all of the inclusion and exclusion criteria but does not have banked tumor tissue or slides must consent to a tumor biopsy described in Section 7.4.16. Patients participating in the Expansion Stage are not required to provide tumor tissue.

8. Clinical laboratory values as specified below before the first dose of study drug:

   - Total bilirubin must be within normal limit range.
   - ALT or AST must be ≤ 1.5 × the upper limit of normal (ULN) ranges.
   - Serum creatinine must be ≤ 1.5 mg/dL and/or creatinine clearance or calculated creatinine clearance ≥ 50 mL/minute (Cockcroft-Gault formula; see Section 14.1).
   - 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.
   - Metabolic fasting glucose must be ≤ 120 mg/dL and fasting triglycerides ≤ 300 mg/dL.

9. 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 the first study drug

administration (for example, if the institutional normal is 50%, subject's LVEF may be as low as 45% to be eligible for the study).

10. Patients must have radiographically or clinically evaluable tumor.

    - In the **Escalation Stage** and **Expansion Stage** of the study, patients must have radiographically or clinically evaluable tumor.

    - In the **Expansion Stage** of the study, patients must have radiographically measurable disease per RECIST guidelines (Version 1.1) or clinically measurable disease for evaluation of antitumor response.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be enrolled in the study.

1. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3. Treatment with any investigational products within 30 days before the first dose of study drug.

4. Previous treatment with MLN1117 and/or MLN0128; previous treatment with dual mTORC1/2 or dual PI3K-mTOR inhibitors.

5. Patients who received previous therapy with PI3K inhibitors or rapalogs will be allowed in the study if all other inclusion/exclusion criteria are met.

6. Diagnosis of primary brain tumor or symptomatic brain metastasis. Patients with brain metastases must be without neurologic dysfunction that would confound the evaluation of neurologic and other AEs.

7. Failed to have recovered (ie, > Grade 1 toxicity or baseline) from the reversible effects of previous anticancer therapies (except alopecia).

8. Have received systemic corticosteroid (inhalers are allowed) within 7 days before the first administration of study drug.

9. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of study drug, including difficulty swallowing capsules.

10. Diagnosis of diabetes mellitus; patients with a history of transient glucose intolerance due to corticosteroid administration are allowed in this study if all other inclusion/exclusion criteria are met.

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

12. Known human immunodeficiency virus infection.

13. 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, or implantable cardiac defibrillator to control rhythm
    - New York Heart Association Class III or IV heart failure (see Section 14.3)
    - Pulmonary embolism

14. 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

15. Baseline prolongation of the rate-corrected QT interval (QTc; eg, repeated demonstration of QTc > 480 msec, or history of congenital long QT syndrome, or torsades de pointes).

16. Patients who are taking PPIs within 7 days of the first dose of MLN0128 + MLN1117 or who require treatment with PPIs throughout the trial or those who are taking H_2 receptor antagonists within 24 hours of the first dose of MLN0128 + MLN1117.

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). MLN0128 and MLN1117 will be administered on an empty stomach. Patients should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose. On Cycle 1, Day 1 and Cycle 1, Day 8, patients will be

required to fast for 2 hours after dosing, until the completion of any scheduled 2-hour postdose fasting glucose, insulin, and insulin C-peptide samples. Each dose of MLN0128 and MLN1117 will be given orally with 8 ounces (240 mL) of water. For information regarding excluded concomitant medications refer to Section 6.7 and the Pharmacy Manual.

Cycle lengths are 28 days in all treatment arms. In Treatment Arm A, MLN0128 will be administered QD every day and MLN1117 will be administered QD on MWF of every week. In Treatment Arm B and Arm C, both MLN0128 and MLN1117 will be administered on MTuW QW.

Patients should be instructed to take their study medication at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. MLN0128 and MLN1117 should always be taken together, at the same time, when dosed on the same day. Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. If a patient fails to take their MLN0128 and/or MLN1117 doses within the time frame specified (± 6 hours of the scheduled dosing time), then the dose should be skipped and considered a missed dose. Patients should record any missed doses in their dosing diary (see the Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

If severe emesis or mucositis prevents the patient from taking scheduled doses, that dose will be skipped. If emesis occurs after study medication ingestion, the dose will not be readministered, and patients should resume dosing at the next scheduled time with the prescribed dosage. Patients should record the occurrence of the emesis in their dosing diaries (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses.

6.1.1 Expansion Stage

An exception to the previous study drug administration schedule occurs in Cycle 1 for patients in the Expansion Stage. The sponsor will determine 1 combination dose and schedule to be evaluated in this stage (ie, either that of Treatment Arm A, Arm B, or Arm C). The modified dosing schedules described in the following allow for plasma PK characterization of MLN0128 in the absence of concomitantly administered MLN1117 and, likewise, PK characterization of MLN1117 in the absence of concomitantly administered MLN0128.

Treatment Arm A: During Cycle 1, patients will be instructed to take MLN0128 every day, except on Days 13 through 19, when the MLN0128 dose will be withheld. MLN1117 will be administered on every MWF, except on Days 1 through 5 when the MLN1117 dose will be withheld. The regular dosing schedule will be followed in subsequent cycles. Refer to Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A).

Treatment Arm B or Arm C: During Cycle 1, patients will be instructed to take MLN0128 on every MTuW, except on Days 15, 16, and 17, when the MLN0128 dose will be withheld. MLN1117 will be administered every MTuW except on Days 1, 2, and 3 when the MLN1117 dose will be withheld. The regular dosing schedule will be followed in subsequent cycles. Refer to Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C).

6.2 Reference/Control Therapy

Not applicable.

6.3 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010.[(1)] These criteria are provided in the Study Manual. DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to treatment with MLN0128 + MLN1117:

- Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting longer than 7 consecutive days in the absence of growth factor support
- Grade 4 neutropenia of any duration accompanied with fever ≥ 38.5°C and/or systemic infection
- Any other ≥ Grade 4 hematologic toxicity
- Inability to administer at least 75% of planned doses of study drug within Cycle 1 due to treatment-related toxicity or delay in the initiation of the subsequent cycle of therapy by more than 14 days due to treatment-related toxicity (lack of adequate recovery of treatment-related hematological or nonhematologic toxicities)
- Any clinically significant occurrence which the investigators and sponsor agree would place patients at undue safety risk

- Any Grade 3 or greater nonhematologic toxicity with the following exceptions:
    - Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all patients should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment)
    - 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 pulse oral steroids, if necessary)

6.4 Dose Escalation Plan

The rationale for the approach to dose escalation is provided in Section 1.4. The dose escalation scheme is shown in Figure 6-1 (and in Table 6-1). The following rules apply to all cohorts as shown in Figure 6-1 (and in Table 6-1).

The dose intervals will adhere to the 3 + 3 traditional escalation rules, starting with the treatment of 3 patients at a planned dose level, as follows:

1. If 0 of 3 patients experiences DLT, dose escalation will proceed to the next higher dose level at which 3 patients will be enrolled.
2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.
3. Escalation will continue if 1 of 6 patients experiences DLT.
4. If 2 or more patients in any dose level experience DLT, dose escalation will stop, and the previous dose level is considered the MTD.

MLN0128 or MLN1117 doses may be escalated up to 100% dose increments until such time that a Grade ≥ 2 treatment-related toxicity is observed. For cohorts where > 200 mg INK1117 is administered, once it is agreed that a toxicity of severity Grade ≥ 2 is likely related to treatment, subsequent dose escalations will occur based on the observed toxicities at increments of 25% to 66%.

This escalation scheme allows for the determination of MTDs in each treatment arm. The MTD for each agent is defined as any dose level that meets the following criteria (after dose escalation has ended):

1. The dose combination has been tested with at least 6 patients.

2. No more than 1 of 6 patients has experienced a DLT during Cycle 1.

In addition, more conservative dose escalation, reduction, or evaluation of intermediate doses of either study drug in any treatment arm, including further escalation of study drug that was previously fixed and expansion of up to 12 patients in an existing dose cohort, are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose–related toxicity, exposure, or pharmacodynamics of MLN0128 + MLN1117. The highest dose evaluated for either agent in combination will not exceed the single-agent MTD (12 mg MLN0128 and 900 mg MLN1117). The RP2Ds will be determined based on the totality of data, including, but not limited to, safety, tolerability, PK, and clinical response.

6.5 Dosing Group Assignments

The starting combination dose in Treatment Arm A was 2 mg MLN0128 and 100 mg MLN1117 (Cohort 1A); the starting combination dose in Treatment Arm B was 6 mg MLN0128 and 100 mg MLN1117 (Cohort 2A). Treatment Arm A and Arm B were planned to be evaluated in series, with the first 2 cohorts from Treatment Arm A (ie, Cohort 1A and Cohort 2A) completing before Cohort 1B of Treatment Arm B began; however dose escalation and the initiation of additional cohorts were stopped because the study drug combination of 4 mg MLN0128 and 100 mg MLN111 administered in Cohort 2A was not tolerable.

As of Protocol Amendment 2, dose escalation will start with 3 patients enrolled in Treatment Arm A, Cohort 3A, in parallel with 3 patients enrolled in Treatment Arm B, Cohort 1B. The safety of Treatment Arm B, Cohort 2B, will be confirmed before Cohort 1C of Treatment Arm C is initiated. Depending on review of safety and tolerability data, an escalation scheme where 1 agent is fixed, while the other agent is escalated, will continue in this manner until MTD is reached for the combination of MLN0128 + MLN1117 for each treatment arm.

The dose of MLN0128 will remain fixed in Treatment Arm A and Arm C; however, in Arm B, MLN0128 dosing will remain fixed for the first 2 cohorts after which point, the dose level will escalate. Concomitantly, MLN1117 dosing will escalate in Treatment Arm A and Arm C; however, in Arm B, after 1 dose escalation between Cohorts 1B and 2B, MLN1117 dosing will remain fixed. The highest dose evaluated for either agent in combination will not exceed the single-agent MTDs. Additionally, the dose of MLN0128 or MLN1117 may be further escalated within a cohort to an intermediate dose level once an MTD of either agent is identified.

Figure 6-1 Dose Escalation Flowchart by Treatment Arm

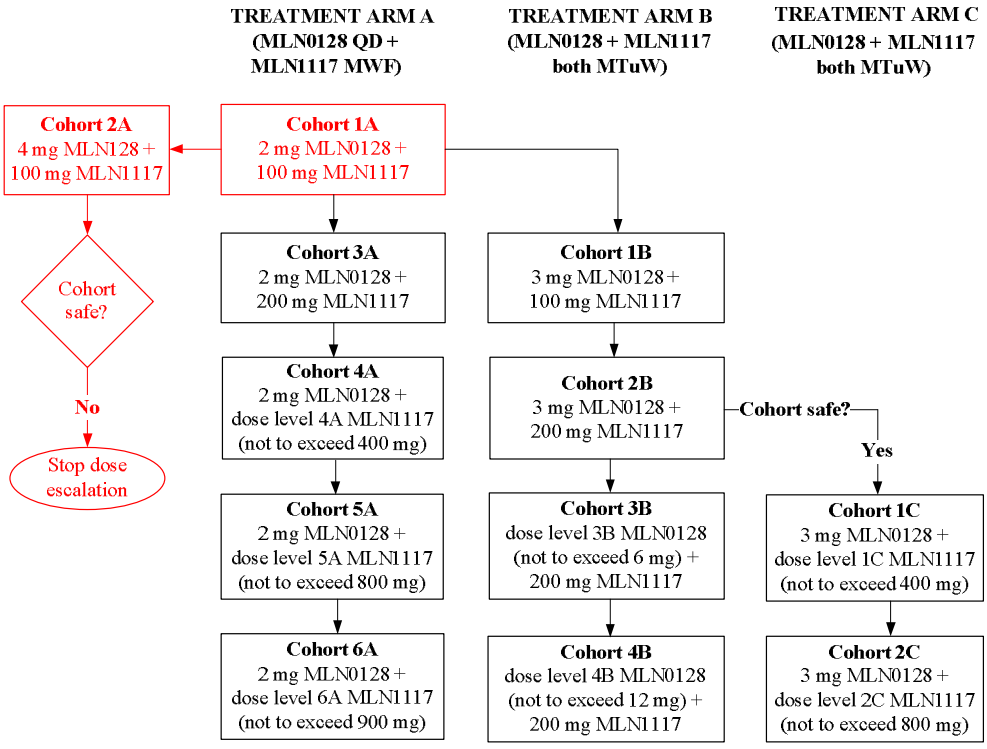


Table 6-1 Dose Escalation Table by Treatment Arm

Treatment Arm A[a] MLN0128 QD + MLN1117 MWF QW			Treatment Arm B[b] MLN0128 + MLN1117 MTuW QW			Treatment Arm C[c] MLN0128 + MLN1117 MTuW QW		
Cohort	**MLN0128**	**MLN1117**	**Cohort**	**MLN0128**	**MLN1117**	**Cohort**	**MLN0128**	**MLN1117**
1A[d]	**2 mg**	**100 mg**		--			--	
2A[d]	**4 mg**	**100 mg**		--			--	
3A	2 mg	200 mg	1B	3 mg	100 mg		--	
4A	2 mg	dose level 4A (not to exceed 400 mg)	2B	3 mg	200 mg		--	
5A	2 mg	dose level 5A (not to exceed 800 mg)	3B	dose level 3B (not to exceed 6 mg)	200 mg	1C	3 mg	dose level 1C (not to exceed 400 mg)
6A	2 mg	dose level 6A (not to exceed 900 mg)	4B	dose level 4B (not to exceed 12 mg)	200 mg	2C	3 mg	dose level 2C (not to exceed 800 mg)

Abbreviations: MTD = maximum tolerated dose; MTuW = Monday, Tuesday, Wednesday; MWF = Monday, Wednesday, Friday; QW = each week.

Shading of dose cohorts across treatment arms indicates those that may be initiated in parallel (eg, enrollment into Cohort 1B and 3A may begin in parallel, enrollment into Cohort 1C and 3B may begin in parallel, etc.). Cohorts 5A, 4B, and 2C are included for reference only. Based on tolerability observed in previous cohorts, cohorts may never be evaluated and cohorts with higher dose levels may be added and escalated according to 3 + 3 rules. Dose increases during escalation are contingent upon the safety observed in the previous cohort and the dose strength available. Once it is agreed that a toxicity of severity Grade ≥ 2 is likely treatment related, subsequent dose escalations will occur based on the observed toxicities at increments of 25% to 66% (eg, dose level 4A and above or cohorts where > 200 mg INK1117 is administered). The highest dose evaluated for either agent in combination will not exceed the single-agent MTD (12 mg MLN0128 and 900 mg MLN1117).

a The dose ofMLN0128 will be fixed at 2 mg and the dose of MLN1117 will be escalated based on observed tolerability.

b Based on tolerability in Cohort 1B, 3 mg MLN0128 + 200 mg MLN1117 will be evaluated in Cohort 2B. Doses of MLN1117 will then be fixed at 200 mg and MLN0128 doses will be escalated based on observed tolerability. Initiation of Cohort 1C does not start until Cohort 2B is determined safe.

c The starting dose of MLN0128 will be 3 mg and the starting dose of MLN1117 will be determined based on tolerability observed in Treatment Arm B. The dose of MLN0128 may be adjusted and the dose of MLN1117 will continue to be escalated based on tolerability.

d Study drug doses in Cohorts 1A and 2A were evaluated under Protocol Amendment 1.

6.6 Dose-Modification Guidelines

6.6.1 General Principles

Treatment cycles with MLN0128 + MLN1117 will occur in 28-day increments. The patient will be evaluated weekly during Cycles 1 and 2, every other week during Cycles 3 and 4, and every cycle thereafter for possible toxicities that may have occurred after the previous dose(s). Toxicity assessment and grading will be based on NCI CTCAE Version 4.03.

For management of toxicity for individual patients, dose adjustment may include interruption of the study drug treatment, a dose reduction of a single agent in the combination (ie, either MLN0128 or MLN1117) or a dose reduction of both agents (ie, MLN0128 and MLN1117). Patients who dose-reduce will not be allowed to re-escalate. Alternative dose modifications may be recommended after discussion with the investigator and the sponsor's project clinician to maximize exposure of study treatment while protecting patient safety.

See Section 6.9 for instructions on managing the following specific clinical events: hyperglycemia (Section 6.9.1.1), hyperlipidemia (Section 6.9.1.2), oral mucositis (Section 6.9.1.3), rash (Section 6.9.1.4), nausea/vomiting (Section 6.9.1.5), cardiac abnormalities (Section 6.9.1.6), AST/ALT elevations (Section 6.9.1.7), and other nonhematologic toxicities (Section 6.9.1.8).

Although DLTs may happen any time during the study, only DLTs occurring during Cycle 1 of the Escalation Stage will impact decisions regarding dose escalation, dose escalation cohort expansion, or intermediate dose level evaluation.

During Cycle 1 of the Escalation Stage, if a patient experiences a DLT (see Section 6.3 for DLT definitions), then treatment will be interrupted and the event will be counted toward the MTD assessment for that dose escalation cohort. Once the toxicity resolves and if the investigator believes the patient will benefit from treatment, then the patient may continue study drug with dose reduction to an established safe dose of MLN0128 + MLN1117. A patient who dose-reduces will not be allowed to re-escalate. Patients enrolled in Cohorts 1A or 1B with DLTs must discontinue from the study. For management of toxicities beyond Cycle 1, see Section 6.6.3

6.6.2 Intrapatient Dose Escalation

Once an MTD has been determined for a respective dosing schedule of MLN0128 + MLN1117, intrapatient dose escalation within this given dosing schedule may be allowed (at the investigator's discretion and with the sponsor's approval) in patients actively receiving MLN0128 + MLN1117 at a dose lower than the MTD, for a minimum of 2 cycles, in the absence of disease progression or unacceptable treatment-related toxicity.

Patients are not allowed to switch from 1 dosing schedule to another or participate in more than 1 treatment arm at any time.

6.6.3 Dose Modification Guidelines

The causal relationship of each AE should be assessed in relation to MLN0128 and in relation to MLN1117 so that dose modifications can be made accordingly. Reduction of 1 agent and not the other is appropriate if toxicity is assessed as primarily related to 1 of the agents. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines.

A decision regarding which study drug requires dose reduction will depend on the toxicity, its onset, and time course. Dosing should be withheld for ≥ Grade 3 MLN0128 - and/or MLN1117-related toxicities. If the event resolves to Grade 1 or baseline values within 14 days of interrupting therapy, the patient may resume combination study treatment if treatment with study drug is thought beneficial by the investigator and with the sponsor's approval based on the guidelines that are provided in Table 6-2. Alternative dose modifications may be recommended after discussion with the investigator and Millennium clinician to maximize exposure of study treatment while protecting patient safety.

Table 6-2 Dose Modification Guidelines for MLN0128 and/or MLN1117 During the Escalation Stage, after Cycle 1, and the Expansion Stage

AE Requiring Dose Modification	Effect on MLN0128 Dose	Effect on MLN1117 Dose
≥ Grade 3 AE primarily related to MLN0128	Dose reduce to next lower dose level	No change
≥ Grade 3 AE primarily related to MLN1117	No change	Dose reduce to next lower dose level
≥ Grade 3 AE related to MLN0128 and MLN1117[a]	No change	Dose reduce to next lower dose level

Abbreviations: AE = adverse event.

a If the initial dose adjustment does not provide sufficient relief, either MLN1117 or MLN0128 can be subsequently reduced.

If the initial dose adjustment does not provide sufficient relief, either MLN1117 or MLN0128 can be subsequently reduced. If MLN0128 + MLN1117 dosing is delayed for > 14 days for MLN0128 and/or MLN1117-related toxicities despite supportive treatment per standard clinical practice or despite more than 2 dose reductions of MLN0128 and 2 dose reductions of MLN1117, following discussions between the sponsor and the investigator, combination therapy must be stopped, the patient discontinued from the study, and the End-of-Study (EOS) visit completed within 30 (+10) days of the last administration of MLN0128 + MLN1117.

The sponsor's clinician should be contacted before any dose modification in MLN0128 or MLN1117 for any patient in the study.

6.6.4 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

+ MLN1117 is administered in continuous cycles, and study drug should be administered continuously unless a Grade 3 or higher MLN0128 and/or MLN1117-related event occurs (See Section 6.6.3).

6.6.5 Causality Assessment Guidance of Adverse Events for MLN0128 and MLN1117

A decision regarding which study drug requires dose reduction will depend on the toxicity, its onset, and time course as well as its potential relatedness to either MLN0128 or MLN1117. Alternative dose modifications may be recommended after discussion with the investigator and sponsor's clinician to maximize exposure of study treatment while protecting patient safety. The assessment of a potential causal relationship of AEs to either MLN0128 and/or MLN1117 should be guided by the underlying single agent clinical experience. A summary of Grade 3 or higher treatment-related AEs occurring in 5% or more of patients in the single-agent data can be used for this guidance and is presented in Table 6-3.

Table 6-3 Guidelines for Assessment of a Potential Causal Relationship Based on Grade 3 or Higher Treatment-Related AEs Occurring in 5% or More of Patients in Each Single-Agent Clinical Program, Respectively

Adverse Event	MLN0128	MLN1117
Stomatitis/Mucosal Inflammation	Yes	No
Rash	Yes	No
Lymphopenia	Yes	No
Hyperglycemia	Yes	No
LFTs (AST/ALT elevation)	No	Yes
Fatigue/Asthenia	Yes	Yes

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFTs = liver function tests.

6.6.6 Criteria for Dose Interruption During a Cycle

If a patient experiences a DLT during Cycle 1 in the Escalation Stage, then treatment should be interrupted and the event will be counted toward the assessment of MTD for the given cohort. Once the toxicity resolves and if the investigator believes the patient will benefit

from treatment, then the patient may continue study drug with dose reduction to an established safe dose of MLN0128 + MLN1117. A patient who dose-reduces will not be allowed to re-escalate. Patients who experience an AE that meets the definition for a DLT during the Escalation Stage after Cycle 1 or during the Expansion Stage should have their study drug treatment interrupted as outlined in Section 6.6.3.

6.6.7 Criteria for Dose Reduction

See Section 6.6.3 for general dose modification guidelines.

6.6.8 Criteria for Discontinuation of MLN0128 + MLN1117

See Section 6.9 for criteria resulting in discontinuation of MLN0128 + MLN1117.

6.7 Excluded Concomitant Medications and Procedures

Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that the risk of a drug-drug interaction between MLN1117 and MLN0128 is considered to be low (see Section 1.5.1.1).

Strong CYP1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator. See Appendix 14.4 for a list of these agents. Alternative treatments, if available, should be considered.

MLN1117 is a poorly soluble drug with inverse pH-dependent solubility (low solubility at higher pH). Due to the potential alteration in MLN1117 absorption by agents that modify gastric pH, the following exclusions or restrictions apply:

- Concomitant administration of any PPI is not permitted during the study. Patients receiving PPI therapy before enrollment must stop using the PPI for 7 days before their first dose of MLN1117. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.

- Histamine H2 receptor antagonists are prohibited during Cycle 1 up to the point of completion of all protocol-specified PK sampling; however, beyond this point of time, histamine H2 receptor antagonists may be allowed, if needed, provided that the histamine H2 receptor antagonist is not taken within 12 hours before MLN1117 dosing and within 6 hours after MLN1117 dosing. Patients receiving histamine H2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of MLN1117. Examples of histamine H2 receptor antagonists

include ranitidine, famotidine, and nizatidine. Cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist (see Appendix 14.4).

- Neutralizing antacid preparations (acid neutralizers) and calcium supplements are not permitted during Cycle 1 on MLN1117 dosing days but may be taken as needed on non-MLN1117 dosing days; however, for all other cycles, administration of both of these agents is permitted except from 2 hours before until 2 hours after MLN1117 dosing. Some antigas preparations may also have antacid properties and should also not be permitted from 2 hours before until 2 hours after MLN1117 administration.

There is potential for MLN1117 to affect the PK of BCRP substrates (eg, methotrexate, imatinib, topotecan, lapatinib, rosuvastatin) as well as OCT1 or OCT2 substrates (eg, metformin, cimetidine, amantadine, famotidine, pindolol; see Section 14.5). Thus, if patients require treatment with medications that are known substrates of these transporters, these agents should be administered with caution or alternate treatment options should be considered. It is recommended that patients requiring metformin for hyperglycemia resulting from MLN0128 + MLN1117 administration begin treatment with the lowest effective dose of metformin and have glycemic levels closely monitored.

6.8 Precautions and Restrictions

No dietary restrictions will be imposed on study patients.

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

It is not known what effects the administration of MLN0128 + MLN1117 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients 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 ICF 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 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.)

6.9 Management of Clinical Events

6.9.1.1 Management of Hyperglycemia

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

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

patients with renal insufficiency. In addition, patients should be encouraged to follow a low carbohydrate diet once hyperglycemia is first observed.

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

Table 6-4 Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
1	Fasting blood sugar > ULN - 160 mg/dL	• Continue close monitoring of blood sugars • Initiate oral hypoglycemic agent	None
2	> 160 - 250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent	None
≥ 3	> 250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin	Hold both MLN0128 and MLN1117 until ≤ Grade 2 Resume MLN0128 + MLN1117 based on timing of recovery after maximal treatment: • ≤ 1 week: resume both drugs at same dose and schedule • > 1 but ≤ 2 weeks: reduce MLN0128 by 1 dose lower and maintain MLN1117 unchanged • > 2 weeks: discontinue subject from the study

Prevention/Prophylaxis:

- Follow fasting glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Most episodes of Grade 1 or 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy at the lowest therapeutic dose is recommended to prevent higher grade hyperglycemia.
- Fasting blood glucose levels ≥ 140 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.

Abbreviations: HbA1c = glycosylated hemoglobin; ULN = upper limit of normal.

6.9.1.2 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided in Table 6-5.

Table 6-5 Management of Hyperlipidemia

Grade	Description	Treatment	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 due to risk of pancreatitis	• Maintain dose if tolerable • If toxicity becomes intolerable, interrupt MLN0128 + MLN1117 dosing until recovery to ≤ Grade 1. Restart at same dose
3	Cholesterol > 400 - 500 mg/dL Triglycerides > 500 - 1000 mg/dL	Same as for Grade 2	Hold MLN0128 + MLN1117 dose until recovery to ≤ Grade 1, then restart MLN0128 with a reduction of 1 dose lower while MLN1117 remains unchanged
4	Cholesterol > 500 mg/dL Triglycerides > 1000 mg/dL	Same as for Grade 2	Discontinue treatment
Prevention/Prophylaxis: Lifestyle modifications, as appropriate (balanced diet, limit alcohol consumption, increase physical activity)			

Abbreviations: ULN = upper limit of normal.

6.9.1.3 Management of Oral Mucositis

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

Table 6-6 Management of Oral Mucositis

Grade	Description	Treatment	Dose Modification
1	Asymptomatic or mild symptoms	• Nonalcoholic mouth wash, or 0.9% salt water rinse • Consider topical corticosteroids at earliest signs of mucositis	None
2	Moderate pain, not interfering with oral intake Modified diet indicated	• Topical analgesic mouth treatments • Topical corticosteroids • Initiate antiviral or antifungal therapy, if indicated	• Maintain MLN0128 dose if tolerable • Hold only MLN0128 dose if intolerable until recovery to ≤ Grade 1, then restart at same dose

Table 6-6 Management of Oral Mucositis

Grade	Description	Treatment	Dose Modification
3	Severe pain, interfering with oral intake	• Same as for Grade 2 • Consider intralesional corticosteroids	• Hold only MLN0128 dose until recovery to ≤ Grade 1, then restart with a reduction of 1 dose lower of MLN0128
4	Life-threatening consequences	• Same as for Grade 2 • Consider intralesional corticosteroids	• Stop MLN0128 + MLN1117and discontinue patient from the study

Prevention/Prophylaxis:

- Initiation of a nonalcoholic mouth wash, or 0.9% salt water rinses 4-6 times daily is strongly recommended at the 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.

6.9.1.4 Management of Rash

Guidance on study drug dose modification for patients with rash is provided in Table 6-7.

Table 6-7 Management of Rash

Grade	Description	Treatment	Dose Modification
≤ 2	Macules/papules covering ≤ 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment and/or oral anti-histamines or antibiotics	None
≥ 3	Macules/papules covering > 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment, oral anti-histamines, oral antibiotics, and/or pulsed steroids	Hold MLN0128 + MLN1117 until ≤ Grade 2 Resume MLN0128 + MLN1117 based on timing of recovery: • ≤ 2 weeks: reduce MLN0128 dose by 1 dose; maintain MLN1117 unchanged • > 2 weeks: stop MLN0128 + MLN1117and discontinue patient from the study

Prevention/Prophylaxis:

- Rash should be managed aggressively. The investigator should consider consulting a dermatologist or other specialist if needed.
- A skin biopsy at the site of rash should be considered as soon as possible after the initial episode.

6.9.1.5 Management of Nausea/Vomiting

Guidance for patients with nausea and/or vomiting is provided in Table 6-8.

Table 6-8 Management of Nausea/Vomiting

Grade	Description	Treatment	Dose Modification
≤ 2	Loss of appetite with or without decreased oral intake 1-5 episodes of vomiting within 24 hours	• Maximize anti-emetic therapy • Consider IV fluid hydration	None
≥ 3	Inadequate oral intake ≥ 6 episodes of vomiting within 24 hours	• Maximize anti-emetic therapy • Initiate tube feeding, IVF or TPN	• Hold MLN0128 + MLN1117 until ≤ Grade 1 • Resume MLN0128 + MLN1117 without dose modification
Prevention/Prophylaxis: Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications are encouraged and may be used before each MLN0128 + MLN1117 dosing as needed throughout the study.			

Abbreviations: IV = intravenous; IVF = intravenous fluids; TPN = total parental nutrition.

6.9.1.6 Management of Cardiac Abnormalities

Management of Patients With Possible Cardiac Instability

For patients showing signs of cardiac instability after MLN0128 + MLN1117 dosing, additional monitoring onsite before clinic discharge should be considered.

Management of Patients With Left Ventricular Dysfunction

Guidance for MLN0128 + MLN1117 dose adjustment for patients with left ventricular dysfunction is provided in Table 6-9.

Table 6-9 Management of Left Ventricular Dysfunction

Grade	Description	Dose Modification
1	Asymptomatic decline in LVEF > 15% from baseline values OR; LVEF > 10%-15% from baseline values and is below institution's LLN	No change; continue MLN0128 + MLN1117 at same dose and schedule.
≥ 2	Symptomatic cardiac dysfunction/congestive heart failure	Discontinue treatment.

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

Management of Patients with QTc Prolongation

Guidance for MLN0128 + MLN1117 dose adjustment for patients exhibiting a prolonged QTc is provided in Table 6-10.

Table 6-10 Management of QTc Prolongation

Grade	Description	Treatment	Dose Modification
2	480 msec < QTc < 501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication, etc.)	None; continue MLN0128 + MLN1117 at the same dose and schedule.
≥ 3	QTc ≥ 501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication)[a]; Consider a formal consult by a cardiologist; Notify the sponsor's medical monitor; Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.	MLN0128 + MLN1117 should be interrupted. The decision whether to reinitiate study drug with or without dose reduction and additional monitoring in those subjects who had asymptomatic prolonged QTc ≥ 501 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated study drug, and appear to have benefitted from treatment with either disease control or response, will be agreed to by the investigator and the medical monitor on a case-by-case basis.

Abbreviations: ECG = electrocardiogram; msec = milliseconds; QTc = QT interval corrected for heart rate.
a A list of medications known to prolong QTc can be found at torsades.org and QTdrugs.org.

The procedures for acquiring and reviewing 12-lead ECGs are given in Section 7.4.12.

6.9.1.7 Management of AST/ALT Elevations

Guidance on dose adjustment for patients with AST/ALT elevations is provided in Table 6-11.

Table 6-11 Management of AST/ALT elevations

Grade	Description	Treatment	Dose Modification
1	> ULN - 3 × ULN	None	None
2	Asymptomatic with levels 3 - 5 × ULN; > 3 × ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia	• Closely monitor LFTs at least weekly or more frequently as indicated • Assess patient for other causes of transaminitis (eg, past medical history, concomitant medications)	None
3	> 5 - 20 × ULN; > 5 × ULN for > 2 weeks	Same as for Grade 2	Hold MLN0128 and MLN1117 until ≤ Grade 1; Restart MLN0128 at the same dose; Restart MLN1117 at a 50% dose reduction
4	> 20 × ULN	Same as for Grade 2	Stop MLN0128 + MLN1117 and discontinue patient from the study
Prevention/Prophylaxis: Ensure proper screening of patients for study participation.			

Abbreviations: LFTs = liver function tests; ULN = upper limit of normal.

6.9.1.8 Management of Other Nonhematologic Toxicities

Guidance on dose adjustment for patients with other nonhematologic toxicities is provided in Table 6-12.

Table 6-12 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Initiate appropriate medical therapy and monitor.	If tolerable, then no adjustment is required.
2	Moderate; minimal, local or noninvasive intervention indicated	Initiate appropriate medical therapy and monitor.	• If tolerable, no adjustment required. • If toxicity becomes intolerable (or ≥ Grade 3), interrupt MLN0128 + MLN1117 dosing until recovery to ≤ Grade 1. Reinitiate combination with a ≥ 1 dose level reduction of MLN1117. If this dose adjustment does not provide sufficient relief, either MLN1117 or MLN0128 can be subsequently reduced.
≥ 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated		Interrupt MLN0128 +MLN1117 dosing until recovery to ≤ Grade 1. Reinitiate combination with a ≥ 1 dose level reduction of MLN1117. If this dose adjustment does not provide sufficient relief, either MLN1117 or MLN0128 can be subsequently reduced.

6.10 Blinding and Unblinding

Not applicable. This is an open-label study.

6.11 Description of Investigational Agents

MLN0128 is available in 1 mg, 3 mg, and 5 mg capsules. MLN1117 is available in 100 mg capsules. See the MLN0128 + MLN1117 IB for full details.

6.12 Preparation, Reconstitution, and Dispensation

MLN0128 and MLN1117 dosage forms will be provided in labeled bottles or blisters in accordance with all applicable regulations. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN0128 and MLN1117 are anticancer drugs, and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 and MLN1117.

6.13 Packaging and Labeling

MLN0128 and MLN1117 are packaged in accordance with all applicable regulations.

6.14 Storage, Handling, and Accountability

All investigational supplies will be kept in a secure area with controlled access and will be stored in their original packaging at labeled conditions. All temperature excursions will be reported to the sponsor. Containers will be kept closed during storage and will be used before the re-test date.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and ICH guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country (where applicable), the Interactive Web Response System provider, and the contract research organization team 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 vulnerable to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

In the Escalation Stage, patients will be divided into treatment arms that differ in combination dosing schedules to determine the MTDs and/or RP2Ds of MLN0128 + MLN1117 in each treatment arm.

Patients in the Expansion Stage will be enrolled into a single treatment arm, the dose and schedule of which will be specified prior to patient enrollment, to examine mutual DDI PK of MLN0128 and MLN1117.

7.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, and EOS. Evaluations during the screening period are to be conducted within 28 days before administration of the first dose of study drug. Procedures conducted during the screening period that are performed within 3 days of Cycle 1, Day 1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified. Unless otherwise noted, evaluations during the treatment period must occur before study drug administration. Tests and procedures should be performed on schedule for all visits. The timing of PK/pharmacodynamic assessments is specified in the Schedule of Events and is not flexible. Laboratory assessments may occur ± 3 days of the scheduled day. All EOS evaluations should occur within 30 (+10) days after the last dose of study drug, or before the start of subsequent antineoplastic therapy.

Refer to the Schedule 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 7.4.9.

7.4.4 Physical Examination

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

7.4.5 Patient Height and Weight

Height will be measured only during screening (within 28 days before the first dose of MLN0128 + MLN1117).

Weight will be measured during the times specified in the Schedule of Events.

7.4.6 Vital Signs

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

7.4.7 ECOG Performance Status

ECOG performance status is to be assessed at the times specified in the Schedule of Events.

7.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test will be performed predose on Cycle 1, Day 1, and negative results must be available before the first dose may be administered. A serum pregnancy test may also be performed within 3 days of dosing in place of the Cycle 1, Day 1 urine test.

7.4.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the electronic case report form (eCRF) from the first dose through 30 days after the last dose. See Section 6.7 for a list of medications and therapies that are prohibited and/or allowed during the study.

7.4.10 Adverse Events

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

7.4.11 Enrollment

A patient is considered to be enrolled in the study when the first dose of MLN0128 + MLN1117 has been administered

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.12 Electrocardiogram

ECGs will be performed locally. A 12-lead ECG will be administered at the time points specified in the Schedule of Events. All scheduled ECGs should be performed after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.

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

If a QTc value is confirmed by a qualified reader as ≥ 501 msec for any ECG, the following will occur:

- The sponsor's clinician will be promptly notified.
- MLN0128 + MLN1117 should be interrupted and an evaluation should be conducted to correct other possible causes (eg, electrolyte disturbance, concomitant medication).

- A formal consultation by a cardiologist should be considered. Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.

The decision whether to reinitiate MLN0128 treatment with or without dose reduction and additional monitoring in those patients who had asymptomatic prolonged QTc ≥ 501 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated MLN0128, and appear to have benefitted from MLN0128 treatment with either disease control or response will be agreed to by the investigator and the sponsor's clinician on a case-by-case basis. See also Section 6.9.1.6.

7.4.13 Echocardiogram or Multiple Gated Acquisition Scan

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

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. Clinical laboratory evaluations will be performed as outlined below:

Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of HbA1c and the following clinical chemistry and hematological parameters will be obtained along with urine samples for urinalysis as specified in the Schedule of Events.

Hematology

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

Chemistry

- Blood urea nitrogen
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase
- Phosphate
- Albumin
- Alkaline phosphatase
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide
- Magnesium
- Amylase

Urinalysis

- Turbidity and Color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Occult Blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes

Coagulation

- Prothrombin time (PT)
- International Normalized Ratio
- Activated partial thromboplastin time (aPTT)

Blood sampling for coagulation assessments will be required within 24 hours before performing any skin biopsy or fresh tumor biopsy.

Fasting Glucose

- Patients are required to fast overnight (nothing except water and/or medications after midnight) or for 8 hours minimum.
- On Cycle 1, Day 1 and Cycle 1, Day 8, patients will be required to fast for 2 hours after dosing, until the completion of the 2 hour postdose fasting glucose sample. On all other dosing days, the patient is only required to fast for 1 hour postdose.
- Samples for fasting glucose will be obtained at the times specified in the Schedule of Events.

Fasting Insulin and Insulin C-Peptide Level

- Patients are required to fast overnight (nothing except water and/or medications after midnight) or for 8 hours minimum.
- On Cycle 1, Day 1 and Cycle 1, Day 8, patients in the Escalation Stage will be required to fast for 2 hours after dosing, until the completion of the 2-hour postdose fasting insulin and insulin C-peptide samples. (The 4-hour and 8-hour postdose blood samples are non-fasting.)

- Samples for fasting insulin and insulin C-peptide levels will be obtained at the times specified in the Schedule of Events.

Fasting Lipid Profile

- Total cholesterol
- Triglycerides
- High density lipoprotein
- Low density lipoprotein

Sampling for the fasting lipid profile will be obtained at the times specified in Schedule of Events.

In-Home Daily Fasting Glucose

- In addition to obtaining fasting glucose levels at the clinic visits as outlined in the Schedule of Events, all patients will be given a glucometer to monitor their daily predose fasting blood glucose levels at home.
- On Cycle 1, Day 2 (Escalation Stage) or Cycle 1, Day 3 (Expansion Stage), the patient will be provided an in-home glucometer. Patients will be trained on proper use of the glucometer and instructed to collect a daily predose fasting glucose level every morning. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.
- The patient will be instructed to contact the site immediately if the value is abnormal (ie, ≥ 140 mg/dL, based on local ULN) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic.
- If no irregularities in the fasting blood glucose level are observed during a minimum of 6 consecutive months, then the frequency of in-home fasting glucose testing may be reduced to twice weekly if the investigator approves. Subjects will continue to notify the investigator of fasting blood glucose levels that exceed 140 mg/dL and, if blood glucose levels are not well controlled or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of fasting blood glucose levels will be reinstated to daily.
- See also Section 6.9.1.1.

7.4.15 Disease Assessment

Patients will undergo computed tomography (CT) with contrast as appropriate, magnetic resonance imaging (MRI), X-ray, and/or bone scanning to monitor and assess disease progression, using RECIST criteria (Version 1.1).[(2)] Contrast CT scans of the chest, abdomen, and pelvis will be obtained at screening. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation

using an imaging modality consistent with that used at screening. Objective assessments will be performed at each time point as described in the Schedule 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 physician's findings will be filed in patient source documents. Exceptions will be made for ovarian or prostate cancer patients with elevated tumor markers in the absence of measurable disease eligible to enroll in the Escalation Stage. Such patients may be evaluated on the basis of CA-125 or prostate-specific antigen, respectively.

7.4.16 Biopsy Samples

During screening, a tumor pathology block (ie, tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) or freshly cut unstained slides, as described in the Study Manual, is required for patients in the Escalation Stage only. If a paraffin-embedded tumor block or unstained slides are not available, the patient will be required to undergo a fresh tumor biopsy at screening as indicated in the Schedule of Events. Patients who undergo biopsy of tumor tissue must have platelet counts greater than or equal to 75,000/mm^3 and normal PT and aPTT within 24 hours before the biopsy and no history of excessive bleeding or of antiplatelet or anticoagulant therapy in the prior 7 days (eg, clopidogrel [Plavix®] or salicylates [aspirin]). The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible. If fresh tumor biopsy collection is unsuccessful, enrollment is contingent upon discussion with the sponsor.

Skin punch biopsies (approximately 2 mm in diameter) will be obtained as specified in Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage) in the Schedule of Events to detect the effect of MLN0128 + MLN1117 on pharmacodynamic markers in the epidermis. On the day of the skin punch biopsy procedure, aPTT and PT must be within the normal range and the platelet count must be ≥ 20,000/mm^3. For skin biopsies on Day 25 of Cycle 1 of the Escalation Stage, aPTT and PT values obtained on Day 24 of Cycle 1 can be used.

The analysis methods of skin and tumor samples are described in Sections 7.4.18 and 7.4.20, respectively. Detailed instructions for collection, processing, and shipment of the skin and fresh tumor biopsy samples are provided in the Study Manual.

7.4.17 PK Assessments

7.4.17.1 Escalation Stage Assessments

In the Escalation Stage, serial PK sampling to characterize the PK of MLN0128 and MLN1117 will occur on the following days in Cycle 1: Day 1 (after first study drug dose) and Day 24 (after study drug dose). Blood sampling will be performed at the times indicated in Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage). When the timing of a PK blood sample coincides with vital sign or ECG measurements, the vital sign or ECG measurement should be obtained before the PK blood sample.

The PK sampling schedules are presented to account for the possibility of either combination dosing schedule (ie, Treatment Arm A, Arm B, or Arm C) being selected in the Expansion Stage.

In addition to the PK sample collections specified, a blood sample to measure MLN0128 and MLN1117 concentrations should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged by the investigator to be treatment-related, irrespective of the cycle, day, or stage of occurrence of the AE. The date and exact time of the unscheduled sample collection should be recorded. Details on the collection, storage, processing, handling, and shipping of PK samples are in the Study Manual.

7.4.17.2 Expansion Stage Assessments

In addition, patients in the Expansion Stage will provide urine samples for PK analysis during Cycle 1 at the time points specified in Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A) and Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C). Samples will be collected as single predose voids and single cumulative 0- to 8-hour postdose duration samples on prespecified days during Cycle 1.

Timing for plasma and urine PK and skin pharmacodynamic assessments is found in Table B: PK Assessment Schedule (Expansion Stage: Treatment Arm A) and Table C: PK Assessment Schedule (Expansion Stage: Treatment Arm B and Arm C). Investigators will be notified as to which treatment arm schedule to follow before the Expansion Stage begins.

Treatment Arm A: MLN0128 QD and MLN1117 MWF QW

PK samples collected on Cycle 1, Day 5 will only be analyzed for MLN0128. MLN1117 plasma concentrations will not be measured in these samples.

PK samples collected on Cycle 1, Day 12 will be analyzed for MLN0128 and MLN1117.

PK samples collected on Cycle 1, Day 19 will only be analyzed for MLN1117. MLN0128 plasma concentrations will not be measured in these samples.

Treatment Arm B and Arm C: MLN1117 and MLN0128 Both Dosed MTuW QW

PK samples collected on Cycle 1, Day 3 will only be analyzed for MLN0128. MLN1117 plasma concentrations will not be measured in these samples.

PK samples collected on Cycle 1, Day 10 will be analyzed for MLN0128 and MLN1117.

PK samples collected on Cycle 1, Day 17 will only be analyzed for MLN1117. MLN0128 plasma concentrations will not be measured in these samples.

The PK sampling and bioanalysis plan will allow for assessment of any DDIs between MLN0128 and MLN1117. Sampling on specified days, when both agents are coadministered, will be used to compare against the single-agent PK when each drug is administered alone in either treatment arm.

7.4.18 Pharmacodynamic Assessments

Skin samples (punch biopsy) are to be collected in the Escalation Stage at the prespecified time points in the Schedule of Events and Table A: PK and Pharmacodynamic Assessment Schedule (Escalation Stage). Techniques used to evaluate the pharmacodynamic effect of MLN0128 + MLN1117 include, but are not limited to, monitoring of phosphorylation of molecules in the PI3K pathway, such as ribosomal protein S6 and AKT, in pre-and postdose samples.

7.4.19 Pharmacogenomic Assessments

DNA extracted from blood samples obtained from all patients at screening will be evaluated for germline polymorphisms in CYP2C9 and CYP2C19 genes and may also be used to assess the impact of genetic polymorphisms on clinically important drug transporters, such as BCRP, organic anion-transporting polypeptide (OATP) 1B1, or OATP1B3, if either MLN0128 or MLN1117 is determined to be substrates of these transporters in future studies. Data from this study may be combined with data from previous and/or future studies to explore the relationship between MLN0128 and MLN1117 PK and the CYP2C9 and CYP2C19 genotypes. DNA samples may be used as a comparator and evaluated for mutations detected in tumor samples.

These analyses are not necessary for study closeout. Detailed instructions for the collection, processing, and shipment of the blood samples are provided in the Laboratory Manual.

7.4.20 Banked (Archived) Tumor Specimen Measurements

Banked formalin-fixed, paraffin-embedded tumor tissue (or fresh tumor biopsy as described in Section 7.4.16) should be obtained from patients in the Escalation Stage at screening for assessment of candidate biomarkers predictive of response, including, but not limited to somatic gene alterations and expression of tumor suppressor genes such as PTEN, tumor proliferation markers such as Ki-67, or diagnostic markers such as estrogen and progesterone receptors. It is anticipated that developing these potential biomarkers of antitumor activity mediated by the combination of MLN0128 and MLN1117 will require analysis of the data from this study in combination with data from other clinical studies of this combination as well as each single agent.

7.5 Completion of Study

Patients will be considered to have completed the study if they (1) complete 1 cycle of treatment with MLN0128 + MLN1117, (2) experience unacceptable toxicity during Cycle 1, or (3) experience progressive disease.

Patients who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced.

In the absence of progressive disease or unacceptable toxicity, patients will be treated for a maximum of 12 months. If beneficial for the patient, then further treatment with MLN0128 + MLN1117 may be permitted upon discussion with the sponsor.

7.6 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Adverse event
- Protocol violation
- Symptomatic deterioration
- Unsatisfactory therapeutic response

- Study terminated by sponsor
- Withdrawal by patient
- Other
- Progressive disease

Within 30 (+10) days of the date of study drug discontinuation, all study procedures outlined for the EOS visit will be completed. The primary reason for study drug discontinuation will be recorded in the eCRF.

Patients who are withdrawn from study during Cycle 1 for reasons other than a 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 and MLN1117 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 and MLN1117 capsules 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. The incidence of DLTs will be tabulated for each dose cohort. Demographic and baseline characteristics will be summarized as appropriate. Analysis of efficacy measures will be descriptive. Disease response of MLN0128 + MLN1117 will be based on the best overall response defined using RECIST 1.1, when feasible. A formal statistical analysis plan will be developed and finalized before database lock.

8.1.1 Determination of Sample Size

To estimate the number of patients for this study, it is assumed that 15% of enrolled patients will be non-evaluable. Approximately 101 patients will be enrolled into this study.

Of the 101 evaluable patients estimated to be enrolled, approximately 81 will be enrolled into the Escalation Stage. These patients will be divided into treatment arms which differ in combination dosing schedules to determine the MTDs and/or RP2Ds of MLN0128 + MLN1117 in each treatment arm. The number of patients enrolled in the Escalation Stage was determined by estimating the number of dose combinations to be evaluated and the number of potential evaluable patients not experiencing a DLT. It is estimated that 3 to 6 patients will be evaluated at each dose level per treatment arm.

After the final doses and schedules have been selected, approximately 20 evaluable patients will be enrolled in the Expansion Stage to evaluate the mutual DDI PK for MLN0128 and MLN1117.

In the Expansion Stage, data from approximately16 of the 20 treated patients must satisfy specific criteria to be included in statistical analysis of the effect of MLN0128 co-administration on MLN1117 PK and the effect of MLN1117 co-administration on MLN0128 PK. If fewer than 16 patients meet these criteria, additional patients will be enrolled in the Expansion Stage to reach a minimum sample size of 16 patients. Specific criteria for inclusion in the statistical analysis are provided in Section 8.1.7.1.

8.1.2 Randomization and Stratification

For the Escalation Stage of the study, patients will be enrolled in successive dose cohorts as described in Section 6.4. No randomization is planned for this study.

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 used for all safety analyses as well as efficacy analyses as data allow.
- PK DDI-evaluable population: Patients from the Expansion Stage with sufficient dosing and concentration-time PK data to reliably estimate PK parameters for statistical analyses of the effect of MLN0128 on MLN1117 PK and the effect of MLN1117 on MLN0128 PK.

- Pharmacodynamics population: Patients with sufficient dosing data in Cycle 1 and sufficient skin or tumor data (collected within the protocol-specified window of sampling time) to reliably measure PD parameters.

- Response-evaluable population: Patients, who receive at least 1 dose of study drug, have measurable disease at baseline, and 1 postbaseline disease assessment will be used for analyses of response.

- DLT-evaluable population: Patients who either experience DLT during Cycle 1, or receive all scheduled doses and complete all study procedures in Cycle 1 without experiencing a DLT.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included 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, body surface area, primary diagnosis, and other parameters as appropriate. No inferential statistics will be conducted.

8.1.6 Efficacy Analysis

Patients will be assessed, if feasible, according to RECIST guidelines. Analysis of efficacy measures will be descriptive. Antitumor activity of MLN0128 + MLN1117 will be based on the best overall response. Investigators will assess response using RECIST guidelines Version 1.1[(2)] at each time point. The best overall response for each patient will be derived programmatically from among the reported responses. Data listings will present the tumor measurements from CT or MRI (including changes from baseline), disease response category (eg, complete response, partial response, stable disease, duration of response and, as appropriate, tumor marker measurements).

8.1.7 PK/Pharmacodynamics/Biomarkers

8.1.7.1 PK Analysis

The following analyses will be performed for patients in the PK population as data allow:

- Plasma concentrations of MLN0128 and MLN1117 will be summarized by time postdose, and grouped by dose group, dosing cycle, and day. Mean and individual plasma concentration-time profiles will be plotted by dose group and dosing cycle and day.

- PK parameters will be calculated for MLN0128 and MLN1117 by noncompartmental analysis as permitted by the data. These parameters will include, but will not be limited to, C_{max}, T_{max}, single-dose end of dosing interval (trough) concentration, AUC_{last}, area under the plasma concentration versus time curve from zero to next dose (AUC_{τ}), $t_{1/2}$, apparent oral clearance, peak-to-trough ratio, renal clearance, and accumulation ratio. As appropriate, these parameters will be summarized by dose group and dosing cycle and day. Dose proportionality of C_{max} and AUC_{τ} may be assessed graphically and by regression analysis using a power model.

Expansion Stage

The following statistical analysis will be performed on PK data acquired in the Expansion Stage. An analysis of variance will be performed with log-transformed C_{max} and AUC_{τ} as the dependent variables, treatment as the fixed effect, and patient as the random effect. Least-square mean ratios between the treatment states (MLN0128+ MLN1117 [Test]) versus MLN0128 or MLN1117 alone [Reference]) will be calculated along with 90% confidence intervals. The comparisons made will depend on the combination dosing schedule that is eventually selected for the Expansion Stage following the determination of the combination MTDs in each treatment arm during the Escalation Stage. Provided below are the options:

MLN0128 QD and MLN1117 MWF QW: Cycle 1, Day 12 (MLN0128 + MLN1117) versus Cycle 1, Day 5 (MLN0128 only) or Cycle 1, Day 19 (MLN1117 only)

MLN1117 and MLN0128 both Administered MTuW QW: Cycle 1, Day 10 (MLN0128 + MLN1117) versus Cycle 1, Day 3 (MLN0128 only) or Cycle 1, Day 17 (MLN1117 only)

A minimum of 16 patients must complete the protocol-specified dosing with both agents and PK assessments to provide sufficient plasma concentration-time data to determine the

MLN0128 and MLN1117 C_{max} and AUC_{last} to be included in statistical analyses of the effect of MLN0128 co-administration on MLN1117 PK and the effect of MLN1117 co-administration on MLN0128 PK.

8.1.7.2 Pharmacodynamic Analysis

Descriptive statistics, graphical methods, and statistical modeling, as appropriate, will be used to explore the relationship between response and the levels of various biomarkers.

As permitted by the data, the relationship between MLN0128 and MLN1117 plasma exposures and levels of skin and tumor pharmacodynamic markers measured by immunohistochemistry may be evaluated graphically to guide understanding of exposure-response relationships.

8.1.7.3 Pharmacogenomic Analysis

Descriptive statistics and graphical methods may be used to explore the relationship between genotypes in drug metabolizing enzymes (and possibly transporters) that contribute to MLN0128 and MLN1117 disposition and selected PK parameters of MLN0128 and MLN1117. Descriptive, statistical, and graphical methods, as appropriate, may also be used to explore the relationship between drug response to the combination and tumor genotype.

8.1.8 Safety Analysis

The incidence of DLT will be tabulated for each dose group. In addition, to assess the relationship between toxicities and MLN0128 + MLN1117 dose levels, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group. The DLT-evaluable population will be used for the analysis of DLT.

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, ECGs, 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.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients)
- SAEs

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

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

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the MLN0128 + MLN1117 safety profile.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of the MLN0128 + MLN1117 combination.

8.1.9 Interim Analysis

No formal interim analysis is planned.

8.2 PK Modeling

MLN0128 and MLN1117 PK data collected in this study, together with PK data collected from previous and future studies, may contribute to population PK analysis. The objectives of this analysis are to understand potential sources of PK variation, including patient-specific covariates (eg, age, gender, and renal and hepatic function) and to enable exploratory analysis of the relationships between PK and drug effects, including pharmacodynamics, clinical response, and safety. If population PK analysis is considered feasible, the specifics of the modeling approaches will be described separately in a population PK analysis plan. Results will be reported separately.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or patient 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 means any untoward medical occurrence in a patient or patient 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

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.[(1)] Clarification should be made between an 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 the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[(1)] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

9.3 Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported from start of dosing on Day 1 of Cycle 1 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 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 banked 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 MedComm Solutions (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.

For Product Complaints, call MedComm Solutions at 1-877-674-3784 (877 MPI DRUG) (for United States and Canada sites) 1-510-740-1273 (international number)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed according to the procedures outlined in Section 9.2.

10.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in 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, and/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. In the event that 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.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

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 + MLN1117 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 + MLN1117 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.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprising Millennium employees and study investigators will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with Millennium.

A prepublication manuscript or abstract is to be provided to Millennium a minimum of 30 days before the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by Millennium of the notification, Millennium shall inform the study centers whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable patient matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Millennium's receipt of the proposed publication to allow time for the filing of patent applications covering patentable patient matter.

- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Millennium's request.

The overall principal investigator will be the last author on abstracts and publications of the data generated from this study. Other authors will be listed according to number of patients enrolled to the study. If the principal investigator has the highest enrollment, he/she may choose to be either first or last author. This policy may be changed with the agreement of both the investigators and Millennium.

12. INVESTIGATOR AGREEMENT

I have read Protocol C32001 Amendment 6: A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) 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 Cockcroft-Gault Equation

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

OR

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

14.2 Eastern Cooperative Oncology Group Scale for Performance Status

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, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[20]

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. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[21]

14.4 List of Relevant Cytochrome P450 Inhibitors and 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 List of Breast Cancer Resistance Protein, Organic Cation Transporter Proteins 1 and 2 Substrates

BCRP, OCT1, and OCT2 Substrates

BCRP Substrates	OCT1 and OCT2 Substrates
Methotrexate	metformin
Imatinib	cimetidine
Topotecan	amantadine
Lapatinib	famotidine
Rosuvastatin	pindolol

14.6 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

The MLN0128 in Combination with MLN1117 C32001 protocol was amended to provide further guidance on use of certain concomitant medications and clarification on the analysis of PK samples in the Mutual DDI PK Expansion Cohort.

Purposes for Amendment 1

The purposes of this amendment were to:

- Provide further guidance on the use of concomitant medications that are substrates of BCRP, OCT1, and OCT2
- Provide clarification on the PK sample analysis in the Mutual DDI PK Expansion Cohort
- Improve the order of assessments in the Schedule of Events table
- Correct an error regarding dose escalation
- Delete a repeated sentence regarding biopsy samples
- Correct typographical errors, punctuation, grammar, and formatting

14.7 Amendment 2 Rationale and Purposes

Rationale for Amendment 2

The primary purpose of this amendment was to adjust the dose escalation schedule on the basis of tolerability data from the initial cohorts (Treatment Arm A, Cohorts 1A and 2A). Dose escalation and the initiation of additional cohorts were stopped because the study drug combination in Cohort 2A was not tolerable. A third treatment arm was added, and the dose escalation plan was updated. On the basis of PK profiles and operational considerations, a third skin biopsy was added. Additionally, cardiac- and pulmonary-related exclusion criteria were updated. The definition of blood glucose (serum versus plasma) and Cycle 1 fasting requirements after study drug administration were clarified. SAE and product complaint reporting information was aligned with current procedures.

Purposes for Amendment 2

The purposes of this amendment were to:

- Add a skin biopsy sample on Cycle 1, Day 24 at 8 hours postdose (Treatment Arm B and Arm C); add a PK sample and skin biopsy (Treatment Arm A) at 2 hours postdose on Cycle 1, Day 25; and specify a window for PK samples when obtained at the same time as skin biopsy samples
- Update data for clinical Study INK1117-001
- Update physiochemical properties of MLN1117

- Add a description of the initial clinical experience with MLN0128 in combination with MLN1117
- Simplify the description of the study rationale, incorporate the protocol amendment rationale on the basis of initial clinical experience with MLN0128 in combination with MLN1117, and incorporate an additional treatment arm (Treatment Arm C)
- Align the primary safety endpoint with corresponding statistical analyses
- Specify the process for selection of the dose and schedule for the Mutual Drug-Drug Interaction PK cohort and the tumor-specific cohorts
- Clarify the number of patients to be enrolled in the study, and remove redundant references to patient numbers throughout the protocol
- Update cardiac- and pulmonary-related exclusion criteria
- Create a separate section for study drug administration instructions for the Mutual Drug-Drug Interaction PK cohort and add links to Table B and Table C in the Schedule of Events
- Adjust the dose escalation plan and dosing group assignments on the basis of initial safety and tolerability data from Treatment Arm A (Cohorts 1A and 2A) and to reflect the addition of Treatment Arm C
- Update dose modification guidelines to align with available capsule strengths
- Clarify the use of concomitant neutralizing antacids on days when study drug is not administered
- Specify the availability of 100 mg capsules only and remove reference to 50 mg capsules of MLN1117
- Remove reference to patients continuing in the study with written permission from the sponsor
- Clarify that on Cycle 1, Day 1 and Cycle 1, Day 8, patients will be required to fast for 2 hours after dosing, until the completion of the 2-hour postdose fasting glucose, insulin, and insulin C-peptide samples
- Specify that the 4-hour and 8-hour postdose blood samples for insulin and insulin C-peptide are nonfasting
- Clarify the definition of blood glucose (serum vs plasma)
- Remove the specification for a minimum of 10 slides of tumor tissue at study entry
- Replace the specification that the consequence of study withdrawal is that no new information will be collected and specify that within 30 days (+ 10 days) of study drug discontinuation, the EOS visit will be completed
- Update SAE reporting information to align with current Millennium standards
- Update product complaints information to align with current Millennium standards
- Add an appendix to specify the Cockcroft-Gault formula for calculated creatinine clearance
- Correct typographical errors, abbreviations, punctuation, grammar, and formatting

14.8 Amendment 3 Rationale and Purposes

Rationale for Amendment 3

The primary purpose of this amendment was to extend the period of contraception duration, based on teratogenic and abortive effects identified during preclinical embryofetal studies in rats. Additionally, SAE and product complaint reporting information was aligned with current procedures. Language referencing the efficacy of MLN0128 compared to approved rapalogs was also removed. When referencing Cohort 2A, the dose evaluated under Protocol Amendment 1, at which the study drug combination was not tolerable, was specified.

Purposes for Amendment 3

The purposes of this amendment were to:

- Delete reference to the efficacy of MLN0128 compared to approved rapalogs
- Specify the dose evaluated in Cohort 2A, under Protocol Amendment 1, at which the study drug combination was not tolerable
- Extend the period of contraception duration from 30 days to 90 days after the last dose of study drug, based on teratogenic and abortive effects identified during preclinical embryofetal studies in rats
- Update SAE reporting information to align with current Millennium standards
- Correct typographical errors, punctuation, grammar, and formatting

14.9 Amendment 4 Rationale and Purposes

Rationale for Amendment 4

The purpose of this amendment was to add an inclusion criterion for LVEF that must be within 5 absolute percentage points of the institutional standard of normal as measured by ECHO or MUGA scan within 4 weeks before the first study drug administration. Additionally, the time before patients must be discontinued from the study for MLN0128- and/or MLN1117-related toxicities was reduced, and the criteria for dose interruption during Cycle 1 of the Escalation Stage was aligned with the general dose modification guidelines. Additionally, assessment windows and values in Section 7.4, Study Procedures, were aligned with the Schedule of Events.

Purposes for Amendment 4

The purposes of this amendment were to:

- Add an inclusion criterion for LVEF within 4 weeks before the first study drug administration and simplify the corresponding study design procedure
- Reduce the time before patients must be discontinued from the study for MLN0128- and/or MLN1117-related toxicities to > 14 days
- Align the criteria for dose interruption during Cycle 1 of the Escalation Stage with general dose modification guidelines such that if a patient experiences a DLT, treatment should be interrupted
- Align ECG rate QTc value with that provided in Table 6-10, Management of QTc Prolongation
- Align the window for EOS assessments in Section 7.4, Study Procedures, with the Schedule of Events
- Specify that if a QTc value ≥ 501 is confirmed, both MLN0128 + MLN1117 should be interrupted
- Align the value that platelet count must be ≥ 20,000/mm^3 for skin biopsies in Section 7.4.16, Biopsy Samples, with the Schedule of Events
- Correct typographical errors, punctuation, grammar, and formatting

14.10 Amendment 5 Rationale and Purposes

Rationale for Amendment 5

The primary purpose of this amendment was to modify the design and assessments for the expansion stage of Study C32001. Design modifications included elimination of the tumor-specific cohorts from the Expansion Stage and reduction of the study's planned sample size to account for this change. Assessment modifications for the Expansion Stage included reduction of 12-lead electrocardiogram (ECG) and glycosylated hemoglobin (HbA1c) frequency, removal of fasting insulin and insulin c-peptide monitoring, and rescheduling of assessments originally planned for Cycle 1, Day 2 to Cycle 1, Day 3.

Purposes for Amendment 5

The specific purposes of this amendment were as follows:

- Remove the tumor-specific cohorts from the expansion stage, update relevant text references and the planned study sample size accordingly, and simplify references to the "mutual drug-drug interaction expansion cohort" to "expansion stage".
- Remove fasting insulin and insulin c-peptide level monitoring during the Expansion Stage.
- Modify the schedule of ECG assessments so that ECGs are conducted only on Days 1, 8, 15, and 22 during the Expansion Stage. Additionally, ECGs scheduled for 4 hours postdose were removed from the planned assessments for the Expansion Stage.
- Reschedule procedures planned for Cycle 1, Day 2 during the Expansion Stage (ie, clinical chemistry assessment, fasting glucose assessment, and distribution of a glucometer for in-home daily fasting glucose monitoring) to Cycle 1, Day 3.
- Clarify that patients participating in the Expansion Stage do not need to provide tumor tissue at screening or skin biopsies for pharmacodynamic assessment.
- Remove HbA1c assessment as part of the chemistry laboratory panel to allow for reduced assessment frequency (ie, at baseline and every 3 cycles thereafter).
- Update the discussions of clinical experience with MLN0128 and MLN1117.
- Correct typographical errors, punctuation, grammar, and formatting.

14.11 Amendment 6 Detailed Summary of Changes

The primary sections of the protocol affected by the changes in Amendment 6 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 #16:

Deleted text: ~~16. Patients who are taking strong or moderate CYP3A4 inhibitors, strong CYP2C9 or CYP2C19 inhibitors or clinically significant inducers of CYPs 3A4, 2C9, or 2C19 within 14 days of the first dose of MLN0128 + MLN1117, or patients who require treatment with these agents during the trial (See Section 6.7 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 for 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 and Procedures:	
Initial wording:	MLN1117 is primarily metabolized by CYP3A4 (72%), with minor contributions from CYPs 1A2 (12%), 2C9 (9%), and 2C8 (6%); whereas, MLN0128 is metabolized by enzymes CYP2C19 (35%), CYP3A4 (28%), and 2C9 (28%). Consequently, induction of CYP3A, 2C19, and 2C9 enzymes by co-administered drugs can potentially result in decreased MLN1117 and MLN0128 exposures with the associated risk of decreased efficacy of MLN1117 and MLN0128. Conversely, inhibition of these enzymes can potentially result in increased MLN1117 and MLN0128 exposures and thus increase the risk for toxicity. Therefore, use of strong and moderate inhibitors of CYP3A, strong inhibitors of CYP2C9, strong inhibitors of CYP2C19, and clinically significant inducers of CYP3A/2C enzymes are not permitted during the study. Accordingly, the following concomitant medications are excluded: • CYP3A, 2C9, and 2C19 inducers: rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, primidone, St. John's Wort, bosentan, nafcillin, and modafinilCYP3A, 2C9, and 2C19 inhibitors: ketoconazole, itraconazole, voriconazole, posaconazole, boceprevir, telaprevir, fluconazole, clarithromycin, telithromycin, troleandomycin, erythromycin, nefazodone, mibefradil, conivaptan, diltiazem, verapamil, dronedarone, aprepitant, casopitant, tofisopam, ciprofloxacin, amiodarone, fluvoxamine, and ticlopidine …. • […]Examples of histamine H2 receptor antagonists include ranitidine, famotidine, nizatidine, and cimetidine.

Amended or new wording:

~~MLN1117 is primarily metabolized by CYP3A4 (72%), with minor contributions from CYPs 1A2 (12%), 2C9 (9%), and 2C8 (6%); whereas, MLN0128 is metabolized by enzymes CYP2C19 (35%), CYP3A4 (28%), and 2C9 (28%). Consequently, induction of CYP3A, 2C19, and 2C9 enzymes by co-administered drugs can potentially result in decreased MLN1117 and MLN0128 exposures with the associated risk of decreased efficacy of MLN1117 and MLN0128. Conversely, inhibition of these enzymes can potentially result in increased MLN1117 and MLN0128 exposures and thus increase the risk for toxicity.~~ **Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that the risk of a drug-drug interaction between MLN1117 and MLN0128 is considered to be low (see Section 1.5.1.1).**

~~Therefore, use of~~ **S**trong ~~and moderate~~ **CYP1A2** inhibitors ~~of CYP3A, strong inhibitors of CYP2C9, strong inhibitors of CYP2C19, and clinically significant~~ **and CYP** inducers **should be administered with caution and at the discretion of the investigator. See Appendix 14.4 for a list of these agents. Alternative treatments, if available, should be considered.** ~~CYP3A/2C enzymes are not permitted during the study. Accordingly, the following concomitant medications are excluded:~~

- ~~CYP3A, 2C9, and 2C19 inducers: rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, primidone, St. John's Wort, bosentan, nafcillin, and modafinil~~
- ~~CYP3A, 2C9, and 2C19 inhibitors: ketoconazole, itraconazole, voriconazole, posaconazole, boceprevir, telaprevir, fluconazole, clarithromycin, telithromycin, troleandomycin, erythromycin, nefazodone, mibefradil, conivaptan, diltiazem, verapamil, dronedarone, aprepitant, casopitant, tofisopam, ciprofloxacin, amiodarone, fluvoxamine, and ticlopidine~~

[…]

- […]Examples of histamine H2 receptor antagonists include ranitidine, famotidine, **and** nizatidine~~, and cimetidine~~. **Cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist (see Appendix 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 Appendix 14.4 List of Relevant Cytochrome P450 Inhibitors and 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: Update the description of potential drug-drug interactions..

The primary change occurs in Section 1.5.1.1 Drug Interaction Risk With :	
Initial wording:	In vitro metabolism experiments using recombinant CYP isoforms have shown that MLN1117 is metabolized by CYPs 3A4, 1A2, 2C8, and 2C9 with relative contributions of 72%, 12%, 6%, and 9%, respectively. Therefore, it is possible that clinically significant inhibitors (eg, strong, moderate inhibitors) or inducers of CYP3A4 may produce increases or decreases in MLN1117 systemic exposures, respectively. Accordingly, concomitant use of strong or moderate CYP3A4 inhibitors/inducers is not permitted in this study.
Amended or new wording:	~~In vitro metabolism experiments using recombinant CYP isoforms have shown that MLN1117 is metabolized by CYPs 3A4, 1A2, 2C8, and 2C9 with relative contributions of 72%, 12%, 6%, and 9%, respectively.~~ **Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that MLN0128 is metabolized primarily via CYP1A2 (approximately 31% to 40%), with a minor contribution from CYP3A4 (approximately 11% to 22%). These data suggest that MLN0128 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-uridine diphosphate glucuronosyltransferase pathway (approximately 18%). The new data differ from the previous in vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in MLN0128 metabolism.** **In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with MLN0128 appears to be low.** Therefore~~, it is possible that clinically significant inhibitors (eg,~~ strong, ~~moderate~~ **CYP1A2**inhibitors~~) or~~ **and CYP** ~~inducers of CYP3A4 may produce increases or decreases in MLN1117 systemic exposures, respectively~~ **(see Appendix 14.4) should only be administered with caution and at the discretion of the investigator during the study. Alternative treatments, if available, should be considered.** ~~Accordingly, concomitant use of strong or moderate CYP3A4 inhibitors/inducers is not permitted in this study.~~

Rationale for Change:
This paragraph was amended to describe updated data on MLN0128 metabolism by specific CYP isoforms.

The following sections also include this change:

- Section 1.5.1.2 Drug Interaction Risk With MLN1117.
- Section 6.7 Excluded Concomitant Medications and Procedures.

Change 5: Remove dietary restrictions related to CYP inhibitors and inducers.

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

Deleted text:

- ~~In addition to the above medications, consumption of grapefruit or grapefruit juice is not permitted during the study. Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study.~~

Rationale for Change:
This 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 6.8 Precautions and Restrictions.
- Appendix 14.4 List of Relevant Cytochrome P450 Inhibitors and Inducers.

Change 6: 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 "u" the Schedule of Events.

Added text: **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.**

Rationale for Change:

The change was made to reduce the burden for long-term patients.

ELECTRONIC SIGNATURES

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