Title: A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer

NCT Number: NCT02725268

Protocol Approve Date: 02 March 2020

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

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

CLINICAL STUDY PROTOCOL C31004 Amendment 06

MLN0128

A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer

Protocol Number:	C31004
Indication:	Advanced solid malignancies
Phase:	2
Sponsor:	Millennium Pharmaceuticals, Inc. 40 Landsdowne Street Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000
EudraCT Number:	2014-005394-37
Therapeutic Area:	Oncology

Protocol History

Original	26 May 2015
Amendment 01	09 February 2016
Amendment 02	19 May 2016
Amendment 03	17 April 2017
Amendment 04	25 September 2017
Amendment 05	23 January 2018
Amendment 06	02 March 2020

Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda."

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

PPD

Signature *Date DD Month YYYY*

Signature *Date DD Month YYYY*

Rationale for Amendment 06

This document describes the changes in reference to the protocol incorporating Amendment 06. The primary purpose of this amendment is to remove long-term follow up (progression-free survival [PFS] and/or overall survival [OS]), clarify study closure, and remove in-home fasting glucose monitoring.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Section 14.12.

Changes in Amendment 06

1. Removed long-term follow up (PFS follow up and/or OS follow up) for patients after end of treatment.
2. Update to the Global Clinical Lead for the study.
3. Removed in-home glucose monitoring.

PROTOCOL SUMMARY

Study Title: A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer

Number of Patients: Approximately 242 patients will be randomized into this study from approximately 75 study centers in North America, Europe, and Asia-Pacific.

Study Objectives

Primary

- To determine if MLN0128 in combination with weekly paclitaxel improves progression-free survival (PFS) compared to weekly paclitaxel alone.

Secondary

- To determine if single-agent MLN0128 improves PFS compared to weekly paclitaxel alone.
- To determine if MLN0128+MLN1117 improves PFS compared to weekly paclitaxel alone.
- To assess the safety and tolerability of single-agent MLN0128, MLN0128 in combination with paclitaxel, and MLN0128+MLN1117.
- To evaluate improvement in efficacy measures (endpoints other than PFS) of MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128+MLN1117 to weekly paclitaxel alone.
- To collect plasma concentration-time data with sparse pharmacokinetic (PK) sampling to contribute to future population PK analysis.

Quality of Life (QOL)

- To assess the QOL and symptoms in patients treated with MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128+MLN1117 to weekly paclitaxel alone.

Exploratory

CCI

[redacted]

Overview of Study Design: This is a phase 2, open-label, randomized, multicenter, 4-arm study of the safety and efficacy of MLN0128 in combination with paclitaxel, single-agent MLN0128, single-agent paclitaxel, and MLN0128 in combination with MLN1117 in adult women with advanced endometrial cancer. The patient population will consist of women with histologic or cytologic diagnosis of endometrial carcinoma (including endometrioid, serous, mixed adenocarcinoma, clear-cell carcinoma, or carcinosarcoma) that is advanced, recurrent, or persistent, and has relapsed or is refractory to curative therapy or established treatments. Patients must have had 1 prior platinum-based chemotherapeutic regimen but not more than 2 prior systemic chemotherapy regimens.

Eligibility will be determined during the Screening period, which may last for up to 28 days before the Cycle 1 Day 1 visit. Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study. Study drug will be administered in 28-day treatment cycles.

Approximately 242 patients will be randomized at a ratio of 1:1:1:1 to receive study drug in one of 4 treatment arms:

- Arm A: paclitaxel 80 mg/m^2 weekly on Days 1, 8, and 15 of a 28-day cycle.
- Arm B: paclitaxel 80 mg/m^2 weekly on Days 1, 8, and 15 of a 28-day cycle+MLN0128 4 mg on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle.
- Arm C: MLN0128 30 mg once weekly (QW) on Days 1, 8, 15, and 22 of a 28-day cycle.
- Arm D: MLN0128 4 mg+MLN1117 200 mg on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle.

In the event that enrollment into a treatment arm(s) is closed, patients will be randomized 1:1 into the remaining treatment arms. Paclitaxel will be administered intravenously (IV), whereas MLN0128 and MLN1117 will be administered by mouth (PO) throughout the study. Patients in Arm A and Arm B will receive paclitaxel alone or paclitaxel+MLN0128 until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients in Arm B who discontinue paclitaxel before disease progression may continue to receive MLN0128 alone until they experience disease progression, unacceptable toxicity, or withdraw consent. In addition, patients will receive MLN0128 (in Arm C) or MLN0128+MLN1117 (in Arm D) continuously until they experience disease progression, unacceptable toxicity, or withdraw consent.

Patients will attend the EOT visit 30 to 40 days after receiving their last dose of study drug.

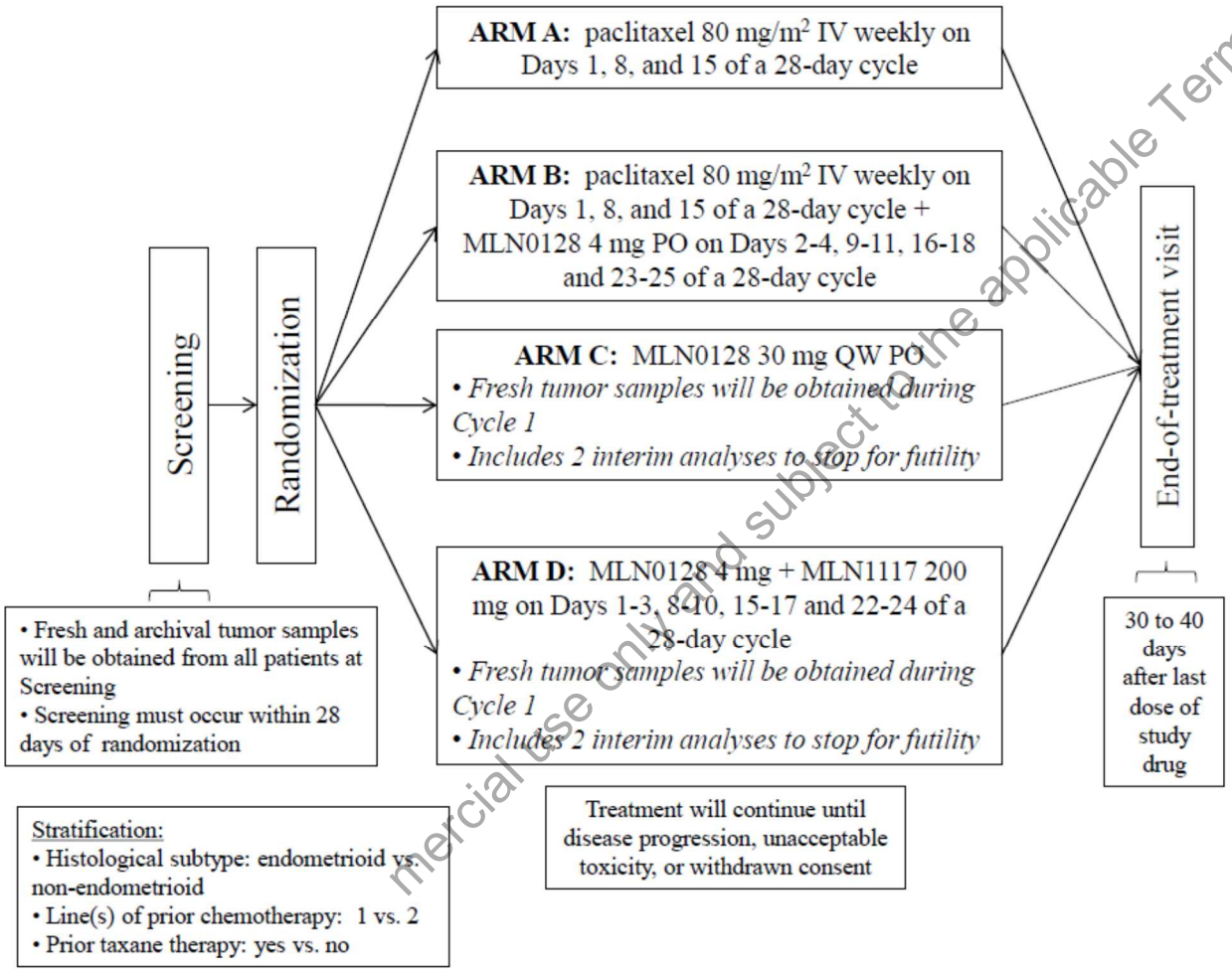
Sparse PK samples will be collected from patients enrolled in Arms B, C, and D for determination of the plasma concentration of MLN0128 and/or MLN1117 during Cycle 1 at prespecified time points. Data generated in this study will be combined with data from other studies in which the PK of MLN0128 is characterized for population PK analysis. For correlative biomarker analysis, fresh and archival tumor samples will be obtained during Screening, CCI at prespecified time points. In addition, fresh tumor samples will be obtained on Cycle 1 Day 22 from patients in Arms C and D to identify adaptive response mechanisms to treatment of MLN0128 or MLN0128+MLN1117.

Radiological tumor evaluations (computed tomography [CT] scan with contrast or magnetic resonance imaging [MRI] with contrast, as clinically indicated) of the chest, abdomen, and pelvis will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).

Changes in QOL disease-specific symptoms will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and the

Endometrial Cancer Module (EORTC QLQ-EN24). Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events. Adverse events will be assessed, and laboratory values, vital signs, and electrocardiograms will be obtained to evaluate the safety and tolerability of MLN0128 in combination with paclitaxel, single-agent MLN0128, and MLN0128+MLN1117. There will be 2 interim analyses with early stopping rules for futility in the single-agent MLN0128 arm (Arm C) and MLN0128+MLN1117 arm (Arm D).
Study Population: Female patients must be 18 years of age or older before the Screening visit to be enrolled in the study. Patients must have histologic or cytologic diagnosis of endometrial carcinoma (including endometrioid, serous, mixed adenocarcinoma, clear-cell carcinoma, or carcinosarcoma), and the cancer is advanced, recurrent, or persistent and has relapsed or is refractory to curative therapy or established treatments. Patients must have had 1 but no more than 2 prior lines of chemotherapy. Patients must have an Eastern Cooperative Oncology Group performance status of 0 to 2 and adequate clinical laboratory values. Patients are required to undergo a fresh tumor biopsy at Screening before beginning study treatment. Patients must have measurable disease by RECIST 1.1 criteria, defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded). Each lesion must be ≥10 mm in long axis when measured by CT, MRI, or caliper measurement by clinical exam. Lymph nodes must be ≥15 mm in short axis when measured by CT or MRI.
Duration of Study: Patients in Arm A and Arm B will receive paclitaxel alone or paclitaxel+MLN0128 until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients in Arm B who discontinue paclitaxel before disease progression may continue to receive MLN0128 alone until they experience disease progression, unacceptable toxicity, or withdraw consent. In addition, patients will receive MLN0128 (in Arm C) or MLN0128+MLN1117 (in Arm D) continuously until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients will discontinue treatment if they have an unacceptable drug-related toxicity. The study will be closed approximately 5 months after the last patient is randomized, or when the last patient discontinues study treatment. Patients will attend an EOT visit 30 to 40 days after receiving their last dose of study drug or at the start of subsequent anticancer therapy. Up until Amendment 06, after EOT, patients were to be followed for PFS and OS, during the Posttreatment follow-up Period.

STUDY OVERVIEW DIAGRAM



Please Note: Up until Amendment 06, after EOT, patients were to be followed for PFS and OS, during the Posttreatment follow-up period.

IV=intravenous(ly), OS=overall survival, PFS=progression-free survival, PO=by mouth, QW=once weekly.

SCHEDULE OF EVENTS

	Screening (a)	TREATMENT CYCLES								
		Cycles 1-8						Cycles 9 and Beyond		
	Day -28 to Day -1	Day 1	Day 3 (b)	Day 8	Day 15	Day 22 (c)	Day 28	Day 1	Day 28	EOT (d)
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Height	X									
Weight	X	X			X			X		X
Physical examination	X	X			X			X		X
Vital signs (e)	X	X		X	X			X		X
ECOG performance status	X	X			X			X		X
Single, 12-lead ECG	X	X (f)						X (f)		X (f)
Histological subtyping	X									
Radiographic tumor evaluation (g)	X						X (g)		X (g)	X (g)
EORTC QLQ-C30 (h)	X	X						X		X
EORTC QLQ-EN24 (h)	X	X						X		X
Monitoring of concomitant medications and procedures		Recorded from the first dose of study drug through 30 days after the last dose of study drug								
Adverse event reporting		Recorded from the first dose of study drug through 30 days after the last dose of study drug								
	Serious adverse events (i) will be reported from signing of the informed consent form through 30 days after the last dose of study drug.									
Dosing (patients will be randomized to one of the following 4 arms) (j):										
Arm A		Paclitaxel 80 mg/m^2 IV weekly on Days 1, 8, and 15 of a 28-day cycle								

	Screening (a)	TREATMENT CYCLES								EOT (d)
		Cycles 1-8						Cycles 9 and Beyond		
	Day -28 to Day -1	Day 1	Day 3 (b)	Day 8	Day 15	Day 22 (c)	Day 28	Day 1	Day 28	
Arm B		Paclitaxel 80 mg/m^2 IV weekly on Days 1, 8, and 15 of a 28-day cycle+MLN0128 4 mg PO on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle								
Arm C		MLN0128 30 mg QW PO								
Arm D		MLN0128 4 mg PO+MLN1117 200 mg PO on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle								
Samples/Laboratory Assessments										
Hematology/chemistry (k)	X1	X1 (l)		X1	X1			X1 (l)		X1
Urinalysis	X1 (m)	X1 (l)						X1 (l)		X1
Pregnancy test (n)	X1	X1 (n)						X1 (n)		
Coagulation (PT/INR, aPTT)	X1	X1 (l)						X1 (l)		X1
Fasting serum glucose (o)	X1	X1						X1		X1
Fasting lipid profile	X1	X1 (p)						X1		X1
HbA1c	X1	X1 (q)						Q3C (q)		
Blood sample for PK analysis (r)		See the Pharmacokinetic Sample Breakdown table								
CCI										
CCI										
Archival (banked) tumor tissue (u)	X1 (u)									
Fresh tumor biopsy (v)	X1 (v)					X1 (c)				

aPTT=activated partial thromboplastin time, CT=computed axial tomography, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, EORTC QLQ-EN24=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer Module, EOT=end of treatment, HbA1c=glycosylated hemoglobin, INR=international normalized ratio, IV=intravenous(ly), MRI=magnetic resonance imaging, OS=overall survival, OSFU=overall survival follow up,

	Screening (a)	TREATMENT CYCLES								
		Cycles 1-8						Cycles 9 and Beyond		
	Day -28 to Day -1	Day 1	Day 3 (b)	Day 8	Day 15	Day 22 (c)	Day 28	Day 1	Day 28	EOT (d)

PFS=progression-free survival, PFSFU=progression-free survival follow up, PK=pharmacokinetic(s), PO=by mouth, PT=prothrombin time, Q=every, QW=once weekly, RECIST=Response Evaluation Criteria in Solid Tumors, X#=the number of samples required (eg, 2 samples=X2).

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days unless otherwise specified) for holidays, vacations, and other administrative reasons, starting after the completion of Cycle 2 Day 1.

(a) Screening assessments are performed within 28 days before the Cycle 1 Day 1 dose. The informed consent form may be signed more than 28 days before Cycle 1 Day 1. 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) The Day 3 visit occurs on Cycle 1 only for PK sample collection from patients in Arm B (MLN0128+paclitaxel) (see the Pharmacokinetic Sample Breakdown table).

(c) The Day 22 visit occurs within Cycle 1 only to obtain fresh, post-dose tumor biopsies from patients in Arm C (single-agent MLN0128) and Arm D (MLN0128+MLN1117) only (see Section 7.4.16 for additional details). The biopsy should be obtained 2-4 hours after study drug dosing.

(d) Patients will attend an EOT visit 30-40 days after receiving their last dose of study drug or at the start of subsequent anticancer therapy, at which time patients will enter posttreatment follow-up. If subsequent anticancer therapy is required before 30 days after the last dose, the EOT visit should be conducted before the initiation of subsequent anticancer therapy. The study will be closed when the last patient discontinues treatment.
Up until Amendment 06, after EOT, patients were to be followed for PFS and OS, during the Posttreatment follow-up period.

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

(f) Single, 12-lead ECGs will be collected predose. When the timing of an ECG coincides with blood samples, the ECG should be completed first.

(g) All CT and MRI scans should be acquired with contrast unless contraindicated for a particular patient. Baseline CT or MRI scans of the chest, abdomen, and pelvis must be obtained within 4 weeks before the first dose of study drug. The same imaging modality (CT or MRI) will be used throughout the study. CT or MRI scans will be obtained every 2 cycles from Cycles 2-8 (ie, Cycle 2 Day 28, Cycle 4 Day 28, Cycle 6 Day 28, and Cycle 8 Day 28 [±3 days]) and then every 3 cycles thereafter (ie, Cycle 11 Day 28, Cycle 14 Day 28, Cycle 17 Day 28 [±5 days], etc), and all Day 28 response assessments should be completed before Day 1 of the subsequent cycle. Up until Amendment 06, a confirmatory scan was to be performed at approximately 4 weeks from the previous scan for all patients with an objective or partial response. A CT or MRI scan is not required at the EOT visit for patients with documented radiographic disease progression.

(h) All questionnaires should be completed before any other study procedures are performed.

(i) Including serious pretreatment events; see Section 9.1.1.

(j) The first dose of study drug must be administered within 5 days after randomization on study. For calculating the appropriate dose of paclitaxel, body surface area should be capped at 2.0 m^2 for all patients receiving paclitaxel in Arm A or Arm B. In Arms B and D, MLN0128 will be administered on an empty stomach; in Arm C, weekly MLN0128 will be administered with a light meal (see Section 6.1).

	Screening (a)	TREATMENT CYCLES								
		Cycles 1-8						Cycles 9 and Beyond		
	Day -28 to Day -1	Day 1	Day 3 (b)	Day 8	Day 15	Day 22 (c)	Day 28	Day 1	Day 28	EOT (d)

(k) Results of hematology and chemistry safety laboratory testing must be available and reviewed by the investigator before enrollment and initial administration of any study drug. For patients randomized to receive paclitaxel (Arms A and B), hematology and chemistry panels are to be tested and reviewed by the investigator or appropriate designee before administering paclitaxel.

(l) May be assessed up to 24 hours before the study visit.

(m) At Screening, creatinine clearance must be ≥50 mL/min based either on Cockroft-Gault estimate or based on a 12- or 24-hour urine collection.

(n) A serum pregnancy test will be performed for women of childbearing potential at Screening. A urine pregnancy test must be performed predose on Day 1 of every cycle with negative results available before the first dose may be administered in that cycle. A serum pregnancy test may also be performed within 3 days before dosing in place of the Day 1 urine test.

(o) Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. For patients in Arm A (single-agent paclitaxel), Arm B (paclitaxel+MLN0128), and Arm C (single-agent MLN0128), the sample will be collected predose; after predose blood draws are complete, patients receiving single-agent MLN0128 QW in Arm C should consume a light meal before dosing (Section 6.1). For patients Arm D (MLN0128+MLN1117), the sample should be taken approximately 2 hours after study drug administration with the patient continuing to fast until the sample is taken.

(p) Fasting lipid profile will be collected at Screening, at Day 1 (predose) of every cycle starting with Cycle 2, and at EOT. A sample is not required at Cycle 1 Day 1.

(q) HbA1c will be evaluated on Day 1 of every 3 cycles (ie, Cycle 3 Day 1, Cycle 6 Day 1, Cycle 9 Day 1, etc).

(r) Blood samples for PK analysis for patients in Arms B, C, and D will be performed according to the schedule presented in the Pharmacokinetic Sample Breakdown table.

(s) CCI [redacted]

(t) CCI [redacted].

(u) Archived tumor tissue from either paraffin blocks or a minimum of 20 unstained slides (paraffin blocks preferred) should be obtained from a previous resection or biopsy that was done as part of the patient's standard care. These samples will be evaluated for candidate biomarkers predictive of response. The archival tumor tissue is to be collected only from enrolled patients and may be collected and sent to the sponsor after initiation of protocol treatment. See Section 7.4.16 for requirements.

(v) Fresh tumor biopsies are required for all patients at Screening. The screening biopsy must be obtained within 14 days before dosing on Cycle 1 Day 1 and should be obtained on a separate visit from the other screening requirements. See Section 7.4.16 for additional details regarding the requirements for tumor biopsies.

PHARMACOKINETIC SAMPLE BREAKDOWN

Treatment Arms B, C, and D Only

	Arm B (Paclitaxel+MLN0128) Only
	Cycle 1 Day 3
Predose	X1
1-2 hours after dose of MLN0128 (a)	X1
3-6 hours after dose of MLN0128 (a)	X1

PK=pharmacokinetic(s), X#=the number of samples required (eg, 2 samples=X2).

(a) On Cycle 1 Day 3, PK plasma specimens can be collected at any time during the sampling window. Over the course of the study, a distribution of sampling times within the windows is encouraged. The exact time and date of MLN0128 dose and the time and date of PK sample collection must be recorded.

	Arm C (Single-Agent MLN0128) Only	
	Cycle 1 Day 1 (a)	Cycle 1 Day 15 (b)
At time of clinic visit (anytime postdose)		X1
Approximately 1 hour after previous PK sample collection		X1
1 to 2 hours postdose (±15 min)	X1	
3 to 6 hours postdose (±30 min)	X2 (c)	

PK=pharmacokinetic(s), X#=the number of samples required (eg, 2 samples=X2).

(a) Patients should bring a light meal with them to this visit. After completion of fasting serum glucose sampling, patients will begin consuming the meal within 30 min before dosing, after which they will take their regularly scheduled doses of MLN0128. The exact date/time of meal consumption, MLN0128 dosing, and PK sampling must be recorded. Over the course of the study, a distribution sampling times is encouraged.

(b) Patients will take their regularly scheduled doses of MLN0128 at home with a light meal and will record the exact date/time of meal consumption and dose administration in their subject diaries. Patients will then report to the clinic for the scheduled visit, during which they will provide PK samples. The exact date/time of PK sampling must be recorded. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged.

(c) Two samples will be taken no less than 1 hr apart within the specified window.

	Arm D (MLN0128+MLN1117) Only	
	Cycle 1 Day 1	**Cycle 1 Day 15**
At time of clinic visit (anytime postdose)		X1 (a)
1 hour (± 10 min) after previous PK sample collection		X1
1-2 hours postdose (b)	X1	
3-6 hours postdose (b)	X1	

PK=pharmacokinetic, X#=the number of samples required (eg, 2 samples=X2).

(a) On Cycle 1 Day 15, patients should take their dose or doses of study drug early in the morning at home and note the exact date and time that the dose was taken. Two postdose PK plasma samples will be collected at the clinic. The first specimen may be collected after arrival at the clinic and the second specimen collected approximately 1 hour after the first. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged. The exact time and date of MLN0128 and MLN1117 dose and the time and date of PK sample collection must be recorded.

(b) On Cycle 1 Day 1, PK plasma samples can be collected at any time during the sampling window. Over the course of the study, a distribution of sampling times within the windows is encouraged. The exact time and date of MLN0128 dose and the time and date of PK sample collection must be recorded.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
4E-BP1	eukaryotic initiation factor 4-binding protein
AE	adverse event
AKT	serine/threonine-specific protein kinase (also known as protein kinase B)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BSA	body surface area
CBR	clinical benefit rate
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CCI	[redacted]
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-EN24	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer Module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment (visit)
HER2	estrogen receptor positive/human epidermal growth factor receptor-2
ER	estrogen receptor
FBG	fasting blood glucose
GCP	Good Clinical Practice
HbA1c	glycosylated hemoglobin, hemoglobin A1c
HDPE	high-density polyethylene
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio

Abbreviation	Term
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IXRS	Interactive Voice/Web Response System
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MLN0128	also known as TAK-228
MLN1117	also known as TAK-117
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian (or mechanistic) target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OCT1	organic cation transporter protein 1
OCT2	organic cation transporter protein 2
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphoinositide-3-kinase, catalytic alpha polypeptide
PK	pharmacokinetic(s)
PO	by mouth (oral)
PPI	proton pump inhibitor
PR	partial response
PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog
PT	prothrombin time
QD	*quaque die*; each day; once daily
QD×3 QW	once daily for 3 days each week
QOL	quality of life
QTc	rate-corrected QT interval (msec)
QTcF	QT interval (msec) with Fridericia correction
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
S473	serine 473
S6K	ribosomal protein S6 kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	Summary of Product Characteristics

Abbreviation	Term
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TORC1	mammalian (or mechanistic) target of rapamycin complex 1
TORC2	mammalian (or mechanistic) target of rapamycin complex 2
TTP	time to progression
ULN	upper limit of the normal range
US	United States
USPI	United States Prescribing Information
WBC	white blood cell

1. BACKGROUND AND STUDY RATIONALE

1.1 Disease Under Treatment

Endometrial cancer is the most common gynecological malignancy with an estimated 287,000 new cases per year worldwide.[1] It is the fourth most common malignancy among women in the United States (US), with an estimated 52,000 new cases and 8,600 deaths in 2013.[2]

Endometrial carcinomas are classified into 2 major types (I and II), based upon light microscopic appearance, clinical behavior, and epidemiology. Type I carcinomas include tumors of endometrioid histology that are Grade 1 or 2. These comprise approximately 80% of endometrial carcinomas and typically have a favorable prognosis, are estrogen responsive, and may be preceded by an intraepithelial neoplasm. Type II tumors account for 10% to 20% of endometrial carcinomas and include Grade 3 endometrioid tumors as well as tumors of nonendometrioid histology (serous, clear-cell, mucinous, squamous, transitional cell, mesonephric, carcinosarcoma, and undifferentiated). These tumors are often high grade, have a poor prognosis, and are not clearly associated with estrogen stimulation. A precursor lesion in type II tumors is rarely identified.

Systemic treatment for metastatic and relapsed endometrial cancer consists of endocrine therapy or cytotoxic chemotherapy. In nonrandomized trials, paclitaxel with carboplatin or cisplatin demonstrated a response rate >60% and a possibly prolonged survival compared with historical experience with other nonpaclitaxel-containing regimens. Results from randomized trials showed a similar response when paclitaxel was added to first-line platinum-containing regimens.[3] Based on these results, paclitaxel-based combination regimens are preferred for first-line chemotherapy of advanced and recurrent endometrial cancer.[4] According to the European Society for Medical Oncology guidelines, endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Various agents have been tested in a number of small phase 2 trials in patients previously exposed to chemotherapy, but the available options and response remain limited.[5] Only high-dose paclitaxel has consistently shown a response rate greater than 20%.

Dose-dense weekly administration of paclitaxel is a proven strategy to further enhance antitumor activity, especially in the re-treatment setting. Preclinical and clinical studies have proven that the duration of paclitaxel exposure is an important determinant of its cytotoxic effect. Thus,

cytotoxicity can be enhanced at fairly low concentrations of paclitaxel provided that the exposure is extended, eg, through weekly administration.[6-8]

1.2 MLN0128

1.2.1 Nonclinical Experience

The mammalian (or mechanistic) target of rapamycin (mTOR) serine/threonine kinase has a central role in regulating cellular growth and metabolism in response to external environmental factors.[9,10] The mTOR kinase binds with other proteins to form 2 distinct multiprotein complexes, mTOR complex 1 (TORC1) and mTOR complex 2 (TORC2). The TORC1 complex is stimulated by growth factors and amino acids and regulates cell growth by controlling the activity of the ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4-binding protein (4E-BP1).[11] The TORC2 complex is activated by growth factors and promotes cell survival, proliferation, and actin cytoskeleton organization by phosphorylating and activating kinases, such as serine/threonine-specific protein kinase (AKT) kinase (also known as protein kinase B), which is a regulator of apoptosis.[12,13]

Two major classes of mTOR inhibitors are under development, allosteric inhibitors and adenosine triphosphate (ATP)-competitive inhibitors. The first-generation, or allosteric, inhibitors include rapamycin and the related analogs or rapalogs temsirolimus, everolimus, and ridaforolimus. The rapalogs effectively inhibit phosphorylation of S6K but only partially inhibit the phosphorylation of 4E-BP1, which regulates cap-dependent translation of transcripts for cell survival, proliferation, and angiogenesis.[10] Thus, rapamycin and the rapalogs are only partial inhibitors of TORC1.[10]

The ATP-competitive inhibitors (also known as mTOR kinase inhibitors or TORKinibs), such as MLN0128, bind to the catalytic domain of mTOR and thus inhibit both TORC1 and TORC2 complexes, including the rapamycin-insensitive or resistant actions of TORC1, such as phosphorylation of 4E-BP1.[14-16]

The rapalogs temsirolimus and everolimus have been approved by the US Food and Drug Administration as monotherapy for patients with advanced renal cell carcinoma (temsirolimus and everolimus), advanced pancreatic neuroendocrine tumors (everolimus), and subependymal giant cell astrocytoma associated with tuberous sclerosis (everolimus). However, resistance to single-agent rapalog therapy occurs and may be related to either incomplete inhibition of the

targeted pathway (such as phosphorylation of 4E-BP1 as discussed previously) or loss of S6K-mediated feedback inhibition of growth factor receptor signaling leading to paradoxical hyperactive signaling. The normal feedback loop involves activated S6K, which phosphorylates and inactivates insulin receptor substrate-1 and inhibits signaling through the phosphoinositide 3-kinase (PI3K) pathway.[13,17] In the presence of rapalogs, the feedback loop is abrogated, leading to continued PI3K signaling, TORC2 activation, and subsequent phosphorylation of AKT at threonine 308 and serine 473 (S473), which markedly enhances the activity of AKT.[10,13,17]

The loss of feedback inhibition by rapalogs has been demonstrated in clinical trials. In an analysis of either paired fresh tumor samples or skin biopsies obtained from 55 patients who received different doses of everolimus either daily or weekly in a phase 1 trial, everolimus inhibited mTORC1 in a dose- and schedule-dependent manner with near complete inhibition of S6K.[18] Half the paired tumor samples had a post-treatment increase in the phosphorylation of AKT at S473.[18] These results provide direct evidence that loss of S6K feedback and subsequent PI3K/TORC2-induced activation of AKT occurs commonly in patients with solid tumors receiving single-agent everolimus.

MLN0128, also known as TAK-228 and INK128, is an orally available, potent, and highly selective ATP competitive inhibitor of mTOR kinase that exhibits dual specificity against both the TORC1 and TORC2 (TORC1/2) complexes.

In vitro studies have demonstrated that MLN0128 selectively and potently inhibits the mTOR kinase (the concentration inhibiting 50% of enzyme activity [IC_{50}] is 1.1 nM). Relative to mTOR inhibition, MLN0128 has >100-fold less potency on class I (PI3K isoforms α, β, γ, δ), class II (PI3KC2α and PI3K2Cβ), and class III (VPS34) PI3K family members. MLN0128 inhibited ligand binding of 10 receptor and intracellular protein kinases (ACVR1, BMPR1B, CSF1R, CSNK1D, CSNK1E, DDR1, MEK1, MEK2, PDGFRB, and RIPK2) out of a panel of 402 distinct kinases. MLN0128 also inhibited the biochemical activity of 5 kinases (mTOR, DNA-PK, PDGFRα, Flt3, and CK1 epsilon kinases) out of a panel of 222 protein kinases by >80% at 1 μM. MLN0128 also displays potent cellular inhibition of both the TORC1 and TORC2 pathway with cellular pharmacodynamically active concentrations at IC_{50} values of less than 10 nM.

MLN0128, administered orally in multiple human tumor xenograft mouse models, can inhibit angiogenesis and tumor growth by inhibiting mTOR signaling at plasma concentrations associated with in vitro inhibition of mTOR in a dose- and time-dependent manner. These effects display a clear pharmacokinetic (PK)-to-pharmacodynamic relationship.[19] MLN0128 inhibits both the phosphorylation of S6 and 4E-BP1, the downstream substrates of TORC1, and selectively inhibits AKT phosphorylation at S473, as evidenced by decreased pAKT, the downstream substrate of TORC2.[19-21] Dual TORC1/2 inhibition mitigates the feedback activation of AKT, which is known to facilitate resistance to TORC1-only inhibitors such as rapamycin.[22] MLN0128 inhibits mTOR signaling and has demonstrated anticancer activity against a number of human solid tumor cell-line xenograft mouse models, including phosphatase and tensin homolog (PTEN) mutant endometrial, breast, and renal cell carcinomas.

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

Clinical Background of the Use of mTOR Inhibitors in Endometrial Cancer

Women with recurrent or metastatic endometrial cancer responded to mTOR inhibition with weekly intravenous (IV) administration of temsirolimus.[23] Response was higher in chemotherapy-naïve patients than those who were chemotherapy-treated. In addition, everolimus showed efficacy as second- or third-line therapy in women with chemotherapy-refractory advanced or metastatic endometrial cancer.[24,25] Also, ridaforolimus showed antitumor activity as second-or third-line therapy in patients with advanced or recurrent endometrial cancer.[23,26,27]

MLN0128 in Combination With Paclitaxel

The mTORC1 inhibitor rapamycin was reported to synergistically enhance the activity of paclitaxel in breast cancer cells.[28] In an AN3-CA endometrial tumor xenograft model, MLN0128 in combination with paclitaxel exhibited stronger antitumor efficacy compared to paclitaxel alone (BIOL-09-011). MLN0128 has been shown to induce G1 cell cycle arrest. Paclitaxel is known to block the progression of cells through G2 into mitosis and this G2-M arrest has been proposed to be a prerequisite step for apoptosis induced by paclitaxel.[29] Pretreatment of mTOR inhibitors will arrest cells in G1 phase and may potentially antagonize the toxic effect of paclitaxel.[30] Therefore, MLN0128 should be given after paclitaxel administration in order not to interfere with the mechanism of paclitaxel.

1.2.2 Clinical Experience

Single-agent MLN0128 is in clinical development with 3 phase 1 studies in patients with either advanced nonhematologic tumors (Studies INK128-001 and C31002) or hematologic malignancies (relapsed or refractory multiple myeloma or Waldenström macroglobulinemia; Study INK128-002). In addition, MLN0128 is being investigated in combination with paclitaxel with or without trastuzumab in a phase 1 study in patients with advanced solid tumors (INK128-003).

Milled MLN0128 is being investigated either as a single agent or in combination with paclitaxel in an additional phase 1 study in patients with advanced solid tumors (Study MLN0128-1004) and in a phase 1/2 study in patients with advanced estrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2)-negative breast cancer (Study C31001). The combination of milled MLN0128 with MLN1117 (an investigational oral PI3Kα inhibitor) is being evaluated in a phase 1b study in adult patients with advanced nonhematologic malignancies (Study C32001).

Further details on these studies are provided in Section 1.4, and in the MLN0128 and MLN0128+MLN1117 IBs.

1.3 MLN0128 in Combination With MLN1117

1.3.1 Nonclinical Experience

Activating somatic missense mutations (eg, E542K, E545K, and H1047R) in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic alpha polypeptide (*PIK3CA*) gene encoding the p110α catalytic subunit of PI3Kα have been identified as a major mechanism for PI3K-dependent malignant transformation, proliferation, and survival. *PIK3CA* mutations have been reported to occur in various solid tumors with the highest rates in breast (27%), endometrial (24%), bladder (23%), colon (15%), and ovarian (10%) cancers.[31-33] In addition to direct mutations of PI3Kα, the pathway may also be activated by mutations or overexpression of upstream effectors such as receptor tyrosine kinases, including HER2, epidermal growth factor receptor, and insulin-like growth factor receptor. *PIK3CA* is also amplified in several tumor types including the squamous type of NSCLC.[34] MLN1117, also known as TAK-117, is a selective, small molecule inhibitor of PI3K. MLN1117 has demonstrated greatest

antiproliferative activity in cell lines harboring *PIK3CA* activating mutations and/or HER2 overexpression.

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/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-adenosine diphosphate 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, PTEN null) and MDA-MB-361 (HER2-amplified breast cancer with mutated PIK3CA), and 1 colorectal cancer HCT-116 (KRAS and PIK3CA mutations) models. MLN0128 and MLN1117 were administered orally (PO) as single agents or in combination concurrently using once daily (QD) 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 drug-drug interactions between MLN0128 and MLN1117 in humans is low.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN1117 and MLN0128+MLN1117 may be found in the current editions of the MLN0128+MLN1117 and MLN1117 IBs.

1.3.2 Clinical Experience

MLN1117 is in clinical development for the treatment of advanced nonhematologic tumors both as a single agent (Study INK1117-001) or in combination with MLN0128 (Study C32001). These studies have been designed to investigate the safety, PK, pharmacodynamics, and preliminary efficacy of MLN1117 either as a single agent or in combination with MLN0128.

Further details are presented in the current editions of the MLN0128+MLN1117 and MLN1117 IBs.

1.4 Study Rationale

The primary objective of this phase 2 study in patients with advanced endometrial cancer is to compare the clinical efficacy of MLN0128+weekly paclitaxel to weekly paclitaxel alone in second- or third-line treatment of advanced, recurrent, or persistent endometrial cancer. In addition, the clinical efficacy of single-agent MLN0128 and the combination of MLN0128+MLN1117 will be compared to weekly paclitaxel alone.

Molecular studies showed that endometrioid neoplasms have a different genetic profile than nonendometrioid neoplasms. Endometrioid carcinomas form 3 subgroups: one with high rates of microsatellite instability, one with POLE mutations leading to ultra-high mutation rates, and one with relatively low mutation rates and exhibiting a microsatellite stable phenotype.[35] Broadly, these tumors are defined by high rate of PTEN mutations and a relative lack of TP53 mutations. Specific mutations in FGFR2, ERBB2, PIK3CA, PIK3R1, KRAS, SOX17 and CTNNB1 (β-catenin) genes are also associated with this tumor type.[35,36] In contrast, serous and serous-like endometrial carcinomas exhibit extensive somatic copy number alterations. Common molecular findings in the serous subtype include p53 and PIK3CA mutations as well as ERBB2 and KRAS amplifications and PTEN deletions.[35,37] Despite these genetic differences between

endometrioid and nonendometrioid carcinomas it is apparent that both histological populations show high rates of genomic alterations of the PI3K-AKT-mTOR pathway that may be sensitive to treatment with a dual TORC1/TORC2 inhibitor such as MLN0128. In addition, the combination of a PI3Kα inhibitor (MLN1117) with a TORC1/2 inhibitor (MLN0128) would be expected to provide more robust inhibition of the PI3K-AKT-mTOR pathway than either agent alone. The randomized, open-label, 4-arm, phase 2 study of paclitaxel, paclitaxel+MLN0128, MLN0128, and MLN0128+MLN1117 will test the following 2 hypotheses: 1) that sequential administration of paclitaxel+MLN0128 can potentiate the cytotoxic effects of paclitaxel and improve treatment outcomes compared to single-agent paclitaxel and 2) that TORC1/2 inhibition either with or without additional PI3Kα inhibition will provide better efficacy compared with the single-agent cytotoxic effects of paclitaxel in patients with advanced recurrent endometrial cancer and progressive disease after platinum-containing cytotoxic chemotherapy.

1.4.1 Rationale for the Proposed Dose and Schedule in Arm B

The selected dose and schedule for Arm B of paclitaxel, 80 mg/m^2 weekly on Days 1, 8, and 15 of each 28-day cycle (weekly paclitaxel)+MLN0128, 4 mg on Days 2-4, 9-11, 16-18, and 23-25 of each 28-day cycle) (QD×3 QW) was determined in 2 designated studies: Study INK128-003 and Study MLN0128-1004.

INK128-003 was an open-label study designed to determine the maximum tolerated dose (MTD) and to identify dose-limiting toxicities (DLTs) for oral administration of unmilled MLN0128 + paclitaxel, with or without trastuzumab, in patients with advanced solid malignancies. In this study, 67 patients with advanced solid tumors received weekly paclitaxel+MLN0128 (6-40 mg via 3 dosing schedules) in the dose-escalation phase (n=47), and weekly paclitaxel+MLN0128 given QD×3 QW with or without trastuzumab 2 mg/kg in the expansion phase (n=20; 5 and 15 patients, respectively).

A favorable tolerability profile was observed when MLN0128 was administered 24 hours after paclitaxel on a QD×3 QW schedule. The MTD for MLN0128 given QD×3 QW in combination with weekly paclitaxel was 10 mg. A dose of 8 mg of MLN0128 was further explored in the expansion phase. The most common Grade 3 or greater study drug-related toxicities observed were neutropenia (21%), diarrhea (12%), and hyperglycemia (12%). Of 54 response-evaluable patients, 8 achieved partial response (PR) and 6 had stable disease (SD) lasting ≥6 months.

MLN0128 exhibited a dose-dependent increase in exposure, and there were no indications of a drug-drug interaction between paclitaxel and MLN0128.

Scale-up manufacturing of MLN0128 required the introduction of a physical milling step to control particle size distribution of MLN0128 drug substance. In order to understand if this milling step altered the safety and PK profile of MLN0128, re-evaluation of safety and PK of the milled MLN0128 dose with weekly paclitaxel to be used in Arm B of this study was conducted in Study MLN0128-1004 under standard phase 1 conditions (see Table 1.a). A total of 22 patients were enrolled and assigned, sequentially, to 2 dosing cohorts at the QD×3 QW dosing schedule for MLN0128+weekly paclitaxel established in Study INK128-003.

Table 1.a DLT Observed with MLN0128 (3 Days Per Week)+Weekly Paclitaxel in Study MLN0128-1004

Dose of Milled MLN0128+Weekly paclitaxel	Number of Evaluable Patients	DLTs Observed in Cycle 1
6 mg QD×3 QW	12	1 patient experienced DLT of fatigue, nausea, dehydration
4 mg QD×3 QW	6	None

While both dose levels were considered safe based on 3+3 rules, the lower dose level of 4 mg QD×3 QW+weekly paclitaxel was chosen as the recommended phase 2 dose (RP2D) of milled MLN0128 for further development.

1.4.2 Rationale for the Proposed Dose and Schedule in Arm C

The selected dose and schedule for Arm C of 30 mg MLN0128 once weekly (QW) is based on the findings from 2 studies: Study INK128-001 and Study MLN0128-1004.

Study INK128-001 was the first-in-human study of MLN0128. Study INK128-001 was an open-label study designed to determine the MTD and to identify DLTs for oral administration of single-agent unmilled MLN0128 and to characterize the safety and tolerability of escalating doses of MLN0128 in patients with advanced solid tumors. In this study, 116 patients with advanced solid tumors received single-agent MLN0128 (2–40 mg via 4 dosing schedules) in the dose escalation phase.

Doses of 40 mg QW, 30 mg QW, and 5 mg QD were further evaluated in an additional 82 patients in the expansion phase.

Improved tolerability, including a reduced frequency of treatment-emergent adverse events (TEAEs) leading to dose interruptions and modifications, respectively (5 mg QD [26% and 67%] vs 30 mg QW [24% and 41%] vs 40 mg QW [19% and 77%] as of a data cut on 09 December 2015), and longer duration of clinical benefit favored 30 mg QW dosing as a RP2D and schedule for further development.

With the introduction of milled MLN0128, the recommended dose to be used in Arm C of this study (30 mg milled MLN0128 QW) was further confirmed in Study MLN0128-1004 (Table 1.b). A total of 14 patients were enrolled and assigned, sequentially, to 2 QW dosing cohorts. PK, safety, and tolerability were assessed.

Table 1.b DLT Observed with Weekly MLN0128 in Study MLN0128-1004

Dose of Milled MLN0128	Number of Evaluable Patients	DLTs Observed in Cycle 1
20 mg QW	6	None
30 mg QW	6	None

As none of the patients in either dose cohort experienced DLT in Cycle 1, a dose of 30 mg MLN0128 QW was selected for further development. No clinically meaningful differences in PK of MLN0128 were noted between the unmilled MLN0128 (Study INK128-001) and milled MLN0128 (Study MLN0128-1004) when given QW.

1.4.3 Rationale for the Proposed Dose and Schedule in Arm D

The dose and schedule selected for Arm D of 4 mg MLN0128+200 mg of MLN1117 (both QD×3 QW) is based on the results of Study C32001 conducted under IND #117,524. Study C32001 is an ongoing open-label study designed to determine the MTD and DLTs for oral administration of milled MLN0128 given in combination with MLN1117 and was designed to characterize the safety and tolerability of escalating doses of MLN0128 and/or MLN1117 in patients with advanced solid tumors. The study features a dose-escalation phase evaluating 3 dosing schedules. A favorable tolerability profile was observed when increasing doses of MLN0128 (3–8 mg) were administered with a fixed dose of MLN1117 (both given QD×3 QW).

The MTD for MLN0128 in combination with MLN1117 both given QD×3 QW was 6 mg MLN0128+200 mg MLN1117.

Table 1.c DLT Observed with MLN0128+MLN1117 (3 Days Per Week) in Study C32001

Dose of Milled MLN0128+MLN1117	Number of Evaluable Patients	DLTs Observed in Cycle 1
6 mg+200 mg QD×3 QW	6	1 patient experienced DLT of AST/ALT elevation
4 mg+200 mg QD×3 QW	8	None

AST=aspartate aminotransferase, ALT=alanine aminotransferase.

While both combination dose levels were considered safe based on 3+3 rules, the lower dose level of 4 mg+200 mg QD×3 QW was chosen as the RP2D for milled MLN0128+MLN1117 for further development.

1.4.4 Rationale for Fresh Tumor Biopsies to Study Adaptive Response

Tumors develop resistance to targeted therapies through various adaptive responses including upregulation of pro-survival signaling and activation of "bypass" signaling pathways.[38] Identifying treatment-induced adaptive response mechanism(s) for a specific therapy has the potential to inform new combination strategies to counter drug resistance. For example, treatment-induced activation of the PI3K/mTOR pathway has been identified as a resistance mechanism for endocrine therapy in breast cancer. Such combination strategy has been tested in the clinic; combination of PI3K/mTOR inhibitor everolimus and endocrine therapy has been tested in clinical trials and shown to derive greater therapeutic benefit than endocrine therapy alone for patients with hormone-receptor positive breast cancer who were previously treated with endocrine therapy.[39,40]

1.5 Potential Risks and Benefits

The most common TEAEs observed with MLN0128 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual mTORC1/2 inhibitors. The TEAEs observed across the MLN0128 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite.

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 the 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 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).

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

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

The benefits of MLN0128 and MLN0128+MLN1117 are discussed in Sections 1.2 and 1.3, respectively.

Further details are presented in the current editions of the MLN0128, MLN0128+MLN1117, and MLN1117 IBs.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is:

- To determine if MLN0128 in combination with weekly paclitaxel improves progression-free survival (PFS) compared to weekly paclitaxel alone.

2.2 Secondary Objectives

The secondary objectives are:

- To determine if single-agent MLN0128 improves PFS compared to weekly paclitaxel alone.
- To determine if MLN0128+MLN1117 improves PFS compared to weekly paclitaxel alone.
- To assess the safety and tolerability of single-agent MLN0128, MLN0128 in combination with paclitaxel, and MLN0128+MLN1117.
- To evaluate improvement in efficacy measures (endpoints other than PFS) of MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128+MLN1117 compared to weekly paclitaxel alone.
- To collect plasma concentration-time data with sparse PK sampling to contribute to future population PK analysis.

2.3 Quality of Life Objective

The quality of life (QOL) objective is:

- To assess the QOL and symptoms in patients treated with MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128+MLN1117 to weekly paclitaxel alone.

2.4 Exploratory Objectives

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[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is:

- PFS.

3.2 Secondary Endpoints

The secondary endpoints are:

- The number and percentage of patients with TEAEs.
- Overall survival (OS).
- Time to progression (TTP).
- Overall response rate (ORR) (complete response [CR]+PR).
- Clinical benefit rate (CBR) (CR+PR+SD, SD of any duration).
- CBR at 16 weeks (CBR-16 is defined as the proportion of patients who achieve CR or PR of any duration or have SD with a duration of at least 16 weeks).

3.3 QOL Endpoints

The QOL endpoints are:

- Change from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) global health status/QOL score to End-of-Study visit.
- Change from Baseline in the EORTC QLQ-C30 functioning score to End-of-Study visit.
- Change from Baseline in the EORTC QLQ-C30 symptom score to End-of-Study visit.
- Change from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer Module (EORTC QLQ-EN24) score to the End-of-Study visit.

3.4 Exploratory Endpoints

The exploratory endpoints are:

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4. STUDY DESIGN

4.1 Overview of Study Design

This study is a phase 2, open-label, randomized, multicenter, 4-arm study of the safety and efficacy of MLN0128 in combination with paclitaxel, single-agent MLN0128, single-agent paclitaxel, and MLN0128 in combination with MLN1117 in adult women with advanced endometrial cancer. The patient population will consist of women with histologic or cytologic diagnosis of endometrial carcinoma (including endometrioid, serous, mixed adenocarcinoma, clear-cell carcinoma, or carcinosarcoma) that is advanced, recurrent, or persistent, that has relapsed or is refractory to curative therapy or established treatments. Patients must have had 1 prior platinum-based chemotherapeutic regimen but not more than 2 prior systemic chemotherapy regimens.

Eligibility will be determined during the Screening period, which may last for up to 28 days before the Cycle 1 Day 1 visit. Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study. Study drug will be administered in 28-day treatment cycles.

Approximately 242 patients will be randomized at a ratio of 1:1:1:1 to receive study drug in one of 4 treatment arms:

- Arm A: paclitaxel 80 mg/m^2 weekly on Days 1, 8, and 15 of a 28-day cycle. For calculation of the paclitaxel dose, body surface area (BSA) is capped at 2.0 m^2.
- Arm B: paclitaxel 80 mg/m^2 weekly on Days 1, 8, and 15 of a 28-day cycle+MLN0128 4 mg on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle. For calculation of the paclitaxel dose, BSA is capped at 2.0 m^2.
- Arm C: MLN0128 30 mg QW on Days 1, 8, 15, and 22 of a 28-day cycle.
- Arm D: MLN0128 4 mg+MLN1117 200 mg on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle.

In the event that enrollment into a treatment arm(s) is closed, patients will be randomized 1:1 into the remaining treatment arms. Paclitaxel will be administered IV while MLN0128 and MLN1117 will be administered PO throughout the study. Patients in Arm A and Arm B will

receive paclitaxel alone or paclitaxel+MLN0128 until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients in Arm B who discontinue paclitaxel before disease progression may continue to receive MLN0128 alone until they experience disease progression, unacceptable toxicity, or withdraw consent. In addition, patients will receive MLN0128 (in Arm C) or MLN0128+MLN1117 (in Arm D) continuously until they experience disease progression, unacceptable toxicity, or withdraw consent.

Patients will attend the EOT visit 30 to 40 days after receiving their last dose of study drug.

Sparse PK samples will be collected from patients enrolled in Arms B, C, and D for determination of the plasma concentration of MLN0128 and/or MLN1117 during Cycle 1 at prespecified time points as described in the Pharmacokinetic Sample Breakdown table. Data generated in this study will be combined with data from other studies in which the PK of MLN0128 is characterized for population PK analysis. For correlative biomarker analysis, fresh and archival tumor samples will be obtained during Screening, CCI [redacted] at prespecified time points as described in the Schedule of Events. In addition, fresh tumor samples will be obtained 2 to 4 hours after dosing on Cycle 1 Day 22 from patients in Arms C and D to identify adaptive response mechanisms to treatment of MLN0128 or MLN0128+MLN1117.

Radiological tumor evaluations (computed tomography [CT] scan with contrast or contrast-enhanced magnetic resonance imaging [MRI], as clinically indicated) of the chest, abdomen, and pelvis will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).[41] Radiographic tumor evaluations will be performed at the time points specified in the Schedule of Events.

Changes in QOL disease-specific symptoms will be assessed using the EORTC QLQ-C30 and the EORTC QLQ-EN24. In addition to assessing selected symptoms, these instruments will measure the effects of disease and treatment on physical, role, emotional, cognitive, and social functioning.

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.[42]

Adverse events (AEs) will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of MLN0128 in combination with paclitaxel, single-agent MLN0128, and MLN0128+MLN1117.

There will be 2 interim analyses with early stopping rules for futility in the single-agent MLN0128 arm (Arm C) and MLN0128+MLN1117 arm (Arm D).

4.2 Number of Patients

Approximately 242 patients will be randomized into this study from approximately 75 study centers in North America, Europe, and Asia-Pacific. A patient will be considered enrolled in the study when they have been randomized into a treatment arm.

4.3 Duration of Study

Patients in Arm A and Arm B will receive paclitaxel alone or paclitaxel+MLN0128 until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients in Arm B who discontinue paclitaxel before disease progression may continue to receive MLN0128 alone until they experience disease progression, unacceptable toxicity, or withdraw consent. In addition, patients will receive MLN0128 (in Arm C) or MLN0128+MLN1117 (in Arm D) continuously until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients will discontinue treatment if they have an unacceptable drug-related toxicity. The study will be closed approximately 5 months after the last patient is randomized, or when the last patient discontinues study treatment.

Patients will attend an EOT visit 30 to 40 days after receiving their last dose of study drug or before the start of subsequent anticancer therapy. Up until Amendment 06, after EOT, patients were to be followed for PFS and OS, during the Posttreatment follow-up period.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Histologic or cytologic diagnosis of endometrial carcinoma (including endometrioid, serous, mixed adenocarcinoma, clear-cell carcinoma, or carcinosarcoma).

2. Evidence that the endometrial cancer is advanced, recurrent, or persistent and has relapsed or is refractory to curative therapy or established treatments.

3. At least 1 prior platinum-based chemotherapeutic regimen, but not more than 2 prior chemotherapeutic regimens, for management of endometrial carcinoma. Prior treatment may include chemotherapy, chemotherapy/radiation therapy, and/or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitized therapy will be considered a systemic chemotherapy regimen.

4. Measurable disease by RECIST 1.1, defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded). Each lesion must be ≥10 mm in long axis when measured by CT, MRI, or caliper measurement by clinical exam. Lymph nodes must be ≥15 mm in short axis when measured by CT or MRI.

5. Tumor accessible and patient consents to undergo fresh tumor biopsies.

6. Female patients 18 years or older.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (refer to Section 14.1).

8. 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 1 highly effective method of contraception and 1 additional effective (barrier) method (see Section 14.2) at the

same time, from the time of signing the informed consent through 90 days (or longer, as mandated by local labeling [eg, United States Prescribing Information (USPI), Summary of Product Characteristics (SmPC), etc]) 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, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9. Clinical laboratory values as specified below within 4 weeks before the first dose of study drug:

   - Bone marrow reserve consistent with absolute neutrophil count (ANC) ≥1500/μL; platelet count ≥100,000/μL; glycosylated hemoglobin (HbA1c) <6.5%.
   - Total bilirubin must be ≤1.5 times the upper limit of the normal range (ULN).
   - ALT or AST must be ≤2.5×ULN. AST and ALT may be elevated up to 5 times the ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in liver.
   - Creatinine clearance ≥50 mL/min/1.73 m^2 based either on Cockcroft-Gault estimate (refer to Section 14.3) or based on a 12- or 24-hour urine collection.
   - Fasting serum glucose <130 mg/dL and fasting triglycerides ≤300 mg/dL.

10. Ability to swallow oral medications, willingness to perform mucositis prophylaxis, and suitable venous access for the study-required blood sampling.

11. 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.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug. Women who are lactating and breastfeeding are not eligible.
2. Previous treatment with any weekly taxane regimen.
3. History of severe hypersensitivity reactions to paclitaxel or any of its excipients.
4. Previous treatment with PI3K, AKT, dual PI3K/mTOR inhibitors, TORC1/2 inhibitors, or TORC1 inhibitors.
5. Initiation of treatment with hematopoietic growth factors, transfusions of blood and blood products, or systemic corticosteroids (either IV or oral steroids, excluding inhalers) within 1 week before administration of the first dose of study drug (patients already receiving erythropoietin on a chronic basis for ≥4 weeks are eligible).
6. Patients who are taking proton pump inhibitors (PPIs) within 7 days of the first dose of study drug 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 study drug.
7. A prothrombin time (PT) or activated partial thromboplastin time (aPTT) above the ULN or a history of a coagulopathy or bleeding disorder.
8. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
9. Sensory or motor neuropathy ≥Grade 2.
10. Central nervous system (CNS) metastasis, endometrial leiomyosarcoma, or endometrial stromal sarcoma.
11. Manifestations of malabsorption due to prior gastrointestinal surgery, gastrointestinal disease, or for some other reason that may alter the absorption of MLN0128 or MLN1117. In addition, patients with enteric stomata are also excluded.

12. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active CNS disease, active infection, or any other condition that could compromise participation of the patient in the study.

13. Known human immunodeficiency virus infection.

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

    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures.
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures.
    - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
    - Placement of a pacemaker for control of rhythm.
    - New York Heart Association Class III or IV heart failure (see Section 14.4).
    - Pulmonary embolism.

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

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

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

16. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

17. Patients with endometrioid histology and histologically confirmed expression of ERs and/or progesterone receptors who have not received prior endocrine therapy and for whom endocrine therapy is currently indicated.

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of MLN0128 or MLN1117 must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

For Arms B and D, 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. Each dose of MLN0128 and MLN1117 will be taken orally with 8 ounces (240 mL) of water.

For Arm C, weekly MLN0128 will be administered with a light meal. Examples of a light meal are provided in Table 6.a. Patients should begin consuming the light meal no more than 30 minutes before taking the weekly dose of MLN0128. It is recommended that each dose of MLN0128 be given PO with 8 ounces (240 mL) of water.

Table 6.a Examples of a Light Meal

	Low-Fat Breakfast	Light Snack
Nutritional information	Approximately 330 calories, with 9 g of fat	Approximately 100-300 calories, with 1.5 g of fat
Example	2 slices of toast with 1 teaspoon of low-fat margarine, 1 teaspoon of jelly, and 8 oz of skimmed milk	3.63 oz pudding cup or 1 slice of toast with 1 teaspoon of jelly and 8 oz of skimmed milk

Cycles consist of 28 days for all treatment arms. In Treatment Arm A, paclitaxel will be administered QW for 3 consecutive weeks (on Days 1, 8, and 15 of a 28-day treatment cycle). In Treatment Arm B, paclitaxel will be administered QW for 3 consecutive weeks (on Days 1, 8, and 15 of a 28-day treatment cycle) and MLN0128 will be administered 3 days per week (on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle). In Treatment Arm C, MLN0128 will be administered QW (on Days 1, 8, 15, and 22 of a 28-day treatment cycle). In Treatment Arm D, MLN0128 and MLN1117 will be administered together, 3 days per week (on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle).

Paclitaxel will be administered IV per its package insert or SmPC.[43,44] For calculating the appropriate dose of paclitaxel, BSA should be capped at 2.0 m^2 for all patients receiving paclitaxel in Arm A or Arm B.

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 does not take their MLN0128 and/or MLN1117 doses within 12 hours after the scheduled dosing time (for patients in Arm B or Arm D) or within 24 hours after the scheduled dosing time (for patients in Arm C), then the dose should be skipped and considered a missed dose. Patients should record any missed doses in their diary (see the Study Manual) and resume drug administration at the next scheduled time with the prescribed dosage.

If severe emesis or mucositis prevents the patient from taking an MLN0128 or MLN1117 dose, that dose will be skipped. If emesis occurs within 6 hours after study medication ingestion, the dose should be counted as missed and will not be re-administered, and patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed

dosage. Patients should record the time of the emesis in their dosing diary (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses.

6.2 Dose Modification Guidelines

The investigator should try to the best of his/her ability to assess whether an AE is possibly related to study drug, and, if so, attribute it to paclitaxel only, MLN0128 only, MLN0128 and paclitaxel, or MLN0128 and MLN1117 and treat the subject accordingly. This section and Table 6.b provide suggested guidelines for the management of various study drug-related toxicities in subjects receiving paclitaxel and MLN0128.

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

All patients who continue to experience any toxicity (hematologic or nonhematologic) of a severity that requires either >3 dose reductions of MLN0128 or >2 dose reductions of paclitaxel, given administration of appropriate supportive care, should discontinue protocol treatment. However, if the patient has evidence of clinical benefit and is considered to possibly benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review by the project clinician. These circumstances should be discussed on a case-by-case basis. As a general rule, if a patient requires dose reduction because of a study drug-related toxicity, the drug dose may not be re-escalated.

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

Paclitaxel. Paclitaxel dosing may be withheld for ≥Grade 2 paclitaxel-related toxicities and resumed at the same dose or at a 20 mg/m^2 dose reduction (25% of starting dose) depending on the timing of recovery and number of episodes occurred (see Table 6.b). If paclitaxel dosing is delayed due to paclitaxel-related toxicities for >21 consecutive days despite supportive treatment per standard clinical practice or more than 2 dose reductions of paclitaxel (≤40 mg/m^2) are required, paclitaxel therapy should be stopped. Please refer to Table 6.b for detailed information on paclitaxel dose reduction/delay for specific AEs.

MLN0128: In general, MLN0128 dosing should be withheld for ≥Grade 3 MLN0128-related nonhematologic toxicities. Table 6.b provides suggested guidelines for the investigator to use along with his/her best judgment for MLN0128 and/or paclitaxel dose delay and/or reduction based on the AE observed. If MLN0128 dosing is delayed because of MLN0128-related toxicities for >21 consecutive days despite supportive treatment per standard clinical practice or if >3 MLN0128 dose reductions are required, stop MLN0128 (and paclitaxel therapy, if applicable), discontinue the subject from the study, and complete the EOT visit within 30 to 40 days of the last administration of MLN0128 or paclitaxel, whichever is discontinued last.

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

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

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

acting myeloid growth factors are preferred, and they should be discontinued for an appropriate number of days before restarting protocol treatment (Table 6.b).

For patients in the single-agent MLN0128 arm (Arm C), up to 3 dose reductions may be applied as shown in Table 6.c.

MLN0128+MLN1117: The primary principle for dose reduction in the MLN0128+MLN1117 arm of the study (Arm D) is to maintain the 200 mg dose of MLN1117, which is considered a minimally efficacious dose in the combination of MLN0128+MLN1117. Thus, the dose of MLN0128 will be reduced if necessary while the dose and schedule of MLN1117 is maintained when study drug administration is resumed (Table 6.c).

If the Grade 3 or greater event that led to dose interruption resolves to Grade 1 or baseline value within 3 weeks of interrupting treatment, then the patient may resume combination study treatment if treatment with study drug is thought to be beneficial for the patient by the investigator and with the sponsor's approval. In this case, the patient may resume study treatment with MLN1117 at 200 mg QD×3 days and MLN0128 reduced by 1 dose level.

Table 6.b Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

AE	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
ANC		
Grade 2 (<1500 - 1000/mm^3)	No change: Continue MLN0128 at same dose and schedule.	• Paclitaxel should not be given to patients who have neutrophil counts of <1500 cells/mm^3 on Day 1 of a 28-day treatment cycle. • Repeat treatment with paclitaxel on Day 8 or Day 15 of a 28-day treatment cycle should be given only if the neutrophil count is ≥1000 cells/mm^3. • If the use of prophylactic myeloid growth factors (ie, GCSF) is considered, GCSF is preferred over peg-filgrastim because of the weekly dosing of paclitaxel in this study. • Growth factor should not be given on the same day as paclitaxel infusion. Growth factor should not be used in the period from 24 hours before through 24 hours after the administration of paclitaxel.

Table 6.b Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

AE	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Grade 3 (<1000 – 500/mm^3)	No change: Continue MLN0128 at same dose and schedule. Consider use of prophylactic myeloid growth factor support per guidelines above.	Hold paclitaxel until ANC ≥1000/mm^3 Resume paclitaxel based on timing of recovery and number of previous episodes: • ≤2 weeks of interrupting planned therapy o First episode: no change to paclitaxel dose. o ≥Second episode: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • >2 weeks of interrupting planned therapy: stop paclitaxel and discontinue subject from study. Consider use of prophylactic myeloid growth factor support per guidelines above.
Grade 4 (<500/mm^3)	Hold MLN0128 until ANC >1000/mm^3 Resume MLN0128 based on timing of recovery: • ≤1 week: no change to MLN0128 dose. • >1 but ≤2 weeks: reduce MLN0128 to the next lower dose level for all subsequent cycles. • >2 weeks: stop MLN0128 and discontinue subject from study. Consider use of prophylactic myeloid growth factor support per guidelines above.	Hold paclitaxel until ANC ≥1000/mm^3 Resume paclitaxel based on timing of recovery and number of previous episodes: • ≤2 weeks of interrupting planned therapy. o First episode: no change to paclitaxel dose. o ≥Second episode: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • >2 weeks of interrupting planned therapy: stop paclitaxel and discontinue subject from study. Consider use of prophylactic myeloid growth factor support per guidelines above.
Thrombocytopenia		
Grade 1 (≥75,000/mm^3)	No change: Continue MLN0128 at same dose and schedule.	No change: Continue paclitaxel at same dose and schedule.
Grade 2 (50,000–74,999/mm^3)	No change: Continue MLN0128 at same dose and schedule.	Hold paclitaxel until platelets >75,000/mm^3 Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • ≤1 week: no change to paclitaxel. • >1 but ≤2 weeks of interrupting planned therapy: reduce paclitaxel by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • >2 weeks of interrupting planned therapy: stop paclitaxel and discontinue subject from study.
Grade 3 (25,000–44,999/mm^3)	Hold MLN0128 until platelets >75,000/mm^3 Resume MLN0128 based on timing of recovery within 2 weeks: • ≤1 week: no change to MLN0128 dose. • >1 but ≤2 weeks: reduce MLN0128 dose to the next lower dose level for all	Hold paclitaxel until platelets >75,000/mm^3. Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • ≤1 week: no change to paclitaxel. • >1 but ≤2 weeks of interrupting planned therapy: reduce paclitaxel dose by 25% from

Table 6.b Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

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

Table 6.b Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

AE	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Grade ≥3	Hold MLN0128 until LFTs improve to ≤Grade 1 or baseline values within 2 weeks. Resume MLN0128 according to the number of episodes that are resolved to ≤Grade 1 or baseline values: • First episode: resume MLN0128 at the same dose and schedule. • Second episode: reduce MLN0128 dose to the next lower dose level for all subsequent cycles. • Third episode: reduce MLN0128 dose to the next lower dose level from the reduced dose for all subsequent cycles. • Fourth episode: stop MLN0128 and discontinue subject from study.	Hold paclitaxel until LFTs improve to ≤Grade 1 or baseline values within 2 weeks of interrupting planned therapy. Resume paclitaxel according to the number of episodes that are resolved to ≤Grade 1 or baseline: • First episode: reduce paclitaxel dose by 25% (60 mg/m^2) from starting dose for all subsequent cycles. • Second episode: resume paclitaxel at the reduced dose (60 mg/m^2) for all subsequent cycles. • Third episode: reduce paclitaxel dose by 50% (40 mg/m^2) from starting dose for all subsequent cycles. • Fourth episode: stop paclitaxel and discontinue subject from study.
Renal (Creatinine)		
Grade 1 (>ULN-1.5×ULN or >1-1.5×baseline)	No change: Continue MLN0128 at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine.	No change: Continue paclitaxel at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine.
Grade 2 (>1.5-3×ULN or >1.5-3.0×baseline)	Hold MLN0128 until creatinine improves to ≤Grade 1 or baseline values in ≤2 weeks. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine. Consider IV hydration. Resume MLN0128 based on timing of recovery: • ≤1 week: no change to MLN0128 dose. • >1 but ≤2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles.	Hold paclitaxel until creatinine improves to ≤Grade 1 or baseline values in ≤2 weeks of interrupting planned therapy. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine. Consider IV hydration. • Resume paclitaxel at the same dose and schedule.

Table 6.b Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

AE	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
	• >2 weeks: stop MLN0128 and discontinue patient from study.	
≥Grade 3 (>3-6×ULN/ >3 baseline or >6×ULN)	Hold MLN0128 until creatinine improves to ≤Grade 1 or baseline values in ≤2 weeks. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine. Consider IV hydration. Resume MLN0128 based on timing of recovery: • ≤1 week: no change to MLN0128 dose. • >1 but ≤2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles. • >2 weeks: stop MLN0128 and discontinue patient from study.	Hold paclitaxel until creatinine improves to ≤Grade 1 or baseline values ≤2 weeks of interrupting planned therapy. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine. Consider IV hydration. Resume paclitaxel based on timing of recovery: • ≤1 week: no change to paclitaxel dose. • >1 but ≤2 weeks of interrupting planned therapy: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • >2 weeks of interrupting planned therapy: stop paclitaxel and discontinue patient from study.
Peripheral Neuropathy		
≤Grade 2	No change: Continue MLN0128 at same dose and schedule.	No change: Continue paclitaxel at same dose and schedule.
≥Grade 3	Continue MLN0128 during the first week when paclitaxel treatment is interrupted. • If peripheral neuropathy does not improve to ≤Grade 2 after 1 week of paclitaxel treatment interruption, hold MLN0128 for 1 week. • Resume MLN0128 at the next lower dose if the event recovers to ≤Grade 2 after 1 week of MLN0128 interruption (2 weeks of paclitaxel interruption). • Stop MLN0128 if the event does not recover to ≤Grade 2 after 1 week of MLN0128 interruption (2 weeks of paclitaxel interruption).	Hold planned paclitaxel for 1 week to see if peripheral neuropathy improves to ≤Grade 2. • Reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles if peripheral neuropathy improves to ≤Grade 2 after 1 week of paclitaxel planned treatment interruption. • If peripheral neuropathy does not improve to ≤Grade 2 after 1 week of planned paclitaxel treatment interruption, continue to hold paclitaxel treatment while MLN0128 treatment is held. • Resume paclitaxel at 25% dose reduction from starting dose (60 mg/m^2) for all subsequent cycles if event recovers to ≤Grade 2 after 2 weeks of paclitaxel interruption (1 week of MLN0128 interruption). • Stop paclitaxel if the event does not recover to ≤Grade 2 after 2 weeks of planned paclitaxel treatment interruption (1 week of MLN0128

Table 6.b Guidelines for MLN0128 and Paclitaxel Dose Modification and Delay

AE	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
		interruption).
Hyperglycemia		
≤Grade 2 (ULN-250 mg/dL)	Continue MLN0128 at same dose and schedule. Refer to Section 6.6.1 for guidelines on hyperglycemia management.	Continue paclitaxel at same dose and schedule. Refer to Section 6.6.1 for guidelines on hyperglycemia management.
≥Grade 3 (>250 mg/dL)	Hold MLN0128 until hyperglycemia improves to Grade ≤2. Refer to Section 6.6.1 for guidelines on hyperglycemia management. Optimize hyperglycemia therapy and resume MLN0128 based on timing of recovery: • ≤1 week: resume MLN0128 at same dose and schedule. • >1 but ≤2 weeks: reduce MLN0128 to the next lower dose. • >2 weeks: stop MLN0128 and discontinue patient from study.	Continue paclitaxel at same dose and schedule. Refer to Section 6.6.1 for guidelines on hyperglycemia management.
Rash		
≤Grade 2	Continue MLN0128 at same dose and schedule. Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	Continue paclitaxel at same dose and schedule. Consider treatment with topical steroid cream/ointment and/or oral antihistamines.
≥Grade 3	Hold MLN0128 until rash improves to Grade ≤2. Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or oral pulse steroids. Refer to Section 6.6.4 for guidelines on management of rash. Resume MLN0128 based on timing of recovery: • ≤2 weeks: reduce MLN0128 to the next lower dose level. • >2 weeks: stop MLN0128 and paclitaxel and discontinue patient from study.	Continue paclitaxel at same dose and schedule. Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or oral pulse steroids.

CRF=case report form, GCSF=granulocyte colony stimulating factor, LFT=liver function test.

Table 6.c Dose Reduction Schedule for MLN0128 and MLN1117

Dose Level	Dose		MLN0128 Capsules: Number and Strength
	MLN0128	MLN1117	
For MLN0128 4 mg QD×3 treatment arm (Arm B) only			
0	4 mg QD×3	-	One 3 mg capsule and one 1 mg capsule
-1	3 mg QD×3	-	One 3 mg capsules
-2	2 mg QD×3	-	Two 1 mg capsules
-3	1 mg QD×3	-	One 1 mg capsule
For MLN0128 30 mg QW treatment arm (Arm C) only			
0	30 mg QW	-	Six 5 mg capsules
-1	20 mg QW	-	Four 5 mg capsules
-2	15 mg QW	-	Three 5 mg capsules
-3	10 mg QW		Two 5 mg capsules
For MLN0128 4 mg QD×3+MLN1117 200 mg treatment arm (Arm D) only			
0	4 mg QD×3	200 mg	One 3 mg capsule and one 1 mg capsule
-1	3 mg QD×3	200 mg	One 3 mg capsules
-2	2 mg QD×3	200 mg	Two 1 mg capsules
-3	1 mg QD×3	200 mg	One 1 mg capsule

6.3 Excluded Concomitant Medications and Procedures

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

6.3.1 Excluded Concomitant Medications for all Patients

The following medications/therapies are prohibited during the study:

- Other investigational agents including mTOR, PI3K, and AKT inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery (patients can have palliative radiation or surgery during the study for pre-existing lesions). Palliative therapy for target lesions is not allowed.

6.3.2 Excluded Concomitant Medications for MLN0128 Single-Agent and Combination Treatment Arms (Arms B, C, and D)

The following medications/therapies are prohibited during the study:

- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of an MLN0128-related AE (eg, rash). Premedication with dexamethasone before paclitaxel administration in this study is allowed. Use of low-dose glucocorticoids for replacement therapy is also allowed.

- Strong and moderate cytochrome P450 (CYP) 1A2 inhibitors, strong CYP3A4 inhibitors, and clinically significant CYP1A2 and CYP3A4 inducers should be administered with caution and at the discretion of the investigator (see Section 14.5 for a list of these agents). Alternative treatments, if available, should be considered.

- Concomitant administration of any PPI is not permitted during the study. Patients receiving PPI therapy before randomization must stop using the PPI for 7 days before their first dose of MLN0128. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.

- Histamine H_2 receptor antagonists are allowed, if needed, provided that the histamine H_2 receptor antagonist is not taken within 12 hours before and within 6 hours after study drug administration. Patients receiving histamine H_2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H_2 receptor antagonists include ranitidine, famotidine, and nizatidine. Cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist (see Section 14.5).

- Administration of neutralizing antacids and calcium preparations is permitted except from 4 hours before until 2 hours after MLN0128 or MLN0128+MLN1117 administration. Some antigas preparations may also have antacid properties and should also not be permitted from 4 hours before until 2 hours after study drug administration.

6.3.3 Potential Drug-Drug Interactions in Arm D (MLN0128+MLN1117)

On the basis of in vitro drug metabolism studies, MLN1117 is primarily metabolized by CYP3A4 (72%), with minor contributions from CYPs 1A2 (12%), 2C9 (9%), and 2C8 (6%).

Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that MLN0128 is metabolized primarily via CYP1A2 (approximately 31%-40%), with a minor contribution from CYP3A4 (approximately 11%-22%). These data suggest that MLN0128 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-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. Neither MLN1117 nor MLN0128 inhibits or induces any of the major CYP enzymes. On the basis of this information, the risk of a drug-drug interaction between MLN1117 and MLN0128 is considered to be low. 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 (Section 14.5) should be administered with caution and at the discretion of the investigator during the study.

There is potential for MLN1117 to affect the PK of breast cancer resistance protein (BCRP) substrates (eg, methotrexate, imatinib, topotecan, lapatinib, rosuvastatin, etc) and organic cation transporter protein (OCT) 1 or OCT2 substrates (eg, metformin, cimetidine amantadine, famotidine, pindolol, etc; see Section 14.6). If patients require treatment with medications that are known substrates of these transporters, then these agents should be administered with caution or alternative treatment options should be considered. It is recommended that patients requiring metformin for treatment of hyperglycemia resulting from MLN0128+MLN1117 administration should begin treatment with the lowest effective dose of metformin and have their blood or serum glucose closely monitored.

6.4 Permitted Concomitant Medications and Procedures

Prophylactic use of antiemetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose and subsequent doses of study drug, as needed throughout the study, and as clinically indicated per standard practice.

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

6.5 Precautions and Restrictions

6.5.1 All Treatment Arms

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with study drug. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, Bacille Calmette-Guerin, yellow fever, varicella, and TY21a typhoid vaccines.

No dietary restrictions will be imposed on study patients (refer to Section 6.3). Patients are required to fast for glucose monitoring (refer to Section 7.4.14 and Section 0). Patients receiving MLN0128 in Arms B or D should refrain from eating or drinking for 2 hours before and 1 hour after each dose (per Section 6.1).

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

Patients should be encouraged to drink at least 20 ounces of fluids a day, especially on days requiring fasting (per protocol), with administration of IV fluids in the clinic as indicated to avoid dehydration.

It is not known what effects MLN0128 or MLN1117 has on human pregnancy or development of the embryo or fetus. Therefore, patients participating in this study should avoid becoming pregnant. Nonsterilized patients of reproductive age group should use effective methods of contraception through defined periods during and after study treatment as specified below.

Patients must meet one 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 1 highly effective method and 1 additional effective (barrier) method of contraception (see Section 14.2), at the same time, from the time of signing of the informed consent form (ICF) through 90 days (or longer, as mandated by local labeling [eg, USPI, SmPC, etc]) 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, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

6.5.2 Paclitaxel (Arm A) and Paclitaxel+MLN0128 (Arm B) Treatment Arms Only

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

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

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

6.6 Management of Clinical Events

6.6.1 Management of Hyperglycemia

Fasting serum glucose levels will be obtained at the clinic visits as outlined in the Schedule of Events. To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines (Table 6.d) are provided to aid the investigator in initiating antiglycemic therapies.

Table 6.d Management of Hyperglycemia

Grade	Description	Treatment	Study Drug Dose Modification
1	FBG >ULN-160 mg/dL	Continue close monitoring of blood glucose. Initiate an oral hypoglycemic agent.	None
2	FBG >160-250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥3	FBG >250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug(s) (a) until ≤Grade 2. Resume study drug(s) based on timing of recovery: • ≤1 week: resume at same dose and schedule. • >1 but ≤2 weeks: reduce the dose of MLN0128 to the next lower dose (see Section 6.2). (b) • >2 weeks: stop study drug.

Prevention/Prophylaxis

- Follow fasting serum glucose levels during clinic visits.
- Check HbA1c levels every 3 months during therapy.
- Recommend lifestyle modifications, as appropriate (balanced diet, limited alcohol consumption, increased physical activity).
- Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy is recommended to prevent higher-grade hyperglycemia.

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117 (Arm D), then both agents should be held.

(b) As described in Section 6.2, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

If any fasting serum glucose reading performed at the site indicates hyperglycemia (>ULN or ≥110 mg/dL), the study staff should first confirm that the patient was fasting at the time of the blood draw (ie, nothing by mouth for at least 8 hours before).

On the basis of the clinical experience in MLN0128 trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with MLN0128, have been Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose limiting since instituting a standard regimen for early treatment of hyperglycemia. All patients developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of patients who

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

It is recommended that patients be treated initially with a fast-acting insulin sensitizer, such as metformin at 500 mg orally QD, and titrate up to a maximum of 1000 mg orally twice daily as needed. Concurrent addition to metformin of dipeptidyl peptidase-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution 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.

6.6.2 Management of Hyperlipidemia

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

Table 6.e Management of Hyperlipidemia

Grade	Description	Treatment	Study Drug Dose Modification
1	Cholesterol: >ULN-300 mg/dL Triglycerides: >150-300 mg/dL	None	None
2	Cholesterol: >300-400 mg/dL Triglycerides: >300-500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥500 mg/dL should be treated urgently because of the risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt study drug(s) (a) dosing until recovery to ≤Grade 1. Reinitiate at same dose.
3	Cholesterol: >400-500 mg/dL Triglycerides: >500-1000 mg/dL	Same as for Grade 2.	Hold dose until recovery to ≤Grade 1, then restart with the next lower dose of MLN0128. (b)
4	Cholesterol: >500 mg/dL Triglycerides: >1000 mg/dL	Same as for Grade 2.	Discontinue treatment.

Prevention/Prophylaxis

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

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117 (Arm D), then both agents should be held.

(b) As described in Section 6.2, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

6.6.3 Management of Oral Mucositis

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

Table 6.f Management of Oral Mucositis

Grade	Description	Treatment	Study Drug 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 dose if tolerable. If toxicity becomes intolerable, interrupt study drug(s) (a) dosing until recovery to ≤Grade 1. Reinitiate at same dose.
3	Severe pain interfering with oral intake	Same as for Grade 2; consider intralesional corticosteroids.	Hold dose until recovery to ≤Grade 1, then restart with the next lower dose level of MLN0128. (b)
4	Life-threatening consequences	Same as for Grade 2; consider intralesional corticosteroids.	Discontinue treatment.

Prevention/Prophylaxis

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

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117 (Arm D), then both agents should be held.

(b) As described in Section 6.2, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

6.6.4 Management of Rash

Patients who develop Grade 4 rash should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity. Grade 4 rash is defined as rash acneiform/papulopustular with papules and/or pustules covering any percentage of BSA, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences (NCI CTCAE version 4.03, effective date 14 June 2010[42]).

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

Table 6.g Management of Rash

Grade	Description	Treatment	Study Drug Dose Modification
≤2	Macules/papules covering ≤30% BSA with or without symptoms.	Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	None
≥3	Macules/papules covering > 30% BSA with or without symptoms.	Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or pulsed steroids.	Hold until ≤Grade 2; resume study drug(s) (a) based on timing of recovery: • ≤3 weeks: reduce dose to the next lower dose level of MLN0128. (b) • >3 weeks: discontinue MLN0128 treatment.

Patients who develop Grade 4 rash should permanently discontinue study treatment unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity. Grade 4 rash is defined as rash acneiform/papulopustular with papules and/or pustules covering any percentage of BSA, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences.

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.

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117 (Arm D), then both agents should be held.

(b) As described in Section 6.2, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

6.6.5 Management of Nausea and/or Vomiting

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

Table 6.h Management of Nausea and/or Vomiting

Grade	Description	Treatment	MLN0128 Dose Modification
≤2	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours.	Maximize antiemetic therapy; consider IV fluid hydration.	None
≥3	Inadequate oral intake; ≥6 episodes of vomiting within 24 hours.	Maximize antiemetic therapy; initiate tube feeding, IVF, or TPN.	Hold until ≤Grade 1; resume study drug(s) (a) without dose modification.

Prevention/Prophylaxis:

- Prophylactic use of antiemetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before each dose of MLN0128 as needed throughout the study.

IVF=intravenous fluids, TPN=total parenteral nutrition.

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117 (Arm D), then both agents should be held.

6.6.6 Management of Cardiac Abnormalities

Management of Patients With Possible Cardiac Instability

For patients showing signs of cardiac instability after MLN0128+MLN1117 administration, 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.i.

Table 6.i 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 study drug(s) (a) at the same dose and schedule.
≥2	Symptomatic cardiac dysfunction/congestive heart failure.	Discontinue treatment.

LLN=lower limit of normal, LVEF=left ventricular ejection fraction.
(a) Study drug(s) refers to MLN0128 and MLN1117. If study drug(s) are to be held, then both agents should be held for patients taking both MLN0128 and MLN1117.

Management of Patients With QTc Prolongation

Guidance for MLN0128+MLN1117 dose adjustment for patients exhibiting a prolonged QTc interval is provided in Table 6.j. Patients who experience persistent Grade 3 or Grade 4 QTc prolongation without another cause should permanently discontinue study treatment.

Table 6.j 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 study drug(s) (a) at the same dose and schedule.
≥3	QTc ≥501 msec or >60 msec change from Baseline	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication). (a) Consider a formal consult by a cardiologist. Notify the sponsor's project clinician. 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.	Hold study drug(s). (b) The decision whether to reinitiate study drug(s) 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 study drug(s), and appear to have benefitted from treatment with either disease control or response, will be agreed to by the investigator and the project clinician on a case-by-case basis. Patients who experience persistent Grade 3 or Grade 4 QTc prolongation without another cause should permanently discontinue study treatment.

(a) A list of medications known to prolong QTc can be found at torsades.org and QTdrugs.org.
(b) Study drug(s) refers to MLN0128 and MLN1117. If study drug(s) are to be held, then both agents should be held for patients taking both MLN0128 and MLN1117.

6.6.7 Management of Other Nonhematologic Toxicities

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

Table 6.k Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Study Drug 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, hold study drug(s) (a) until recovery to ≤Grade 1 then reinitiate at same dose.
≥3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.		Hold study drug(s) until recovery to ≤Grade 1. Reinitiate study drug(s) with the dose of MLN0128 reduced by 1 level (Section 6.2). (b)

(a) Study drug(s) refers to MLN0128 and MLN1117. If study drug(s) are to be held, then both agents should be held for patients taking both MLN0128 and MLN1117.

(b) As described in Section 6.2, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

6.6.8 Management of AST/ALT Elevations

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

Table 6.l Management of AST/ALT Elevations

Grade	Description	Treatment	Study Drug 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 to 20×ULN; >5×ULN for >2 weeks.	Same as for Grade 2.	Hold study drug(s) (a) until ≤Grade 1; restart MLN0128 and MLN1117 at the same doses.
4	>20×ULN.	Same as for Grade 2.	Discontinue treatment with study drug(s).
Prevention/Prophylaxis: Ensure proper screening of patients for study participation.			

LFT=liver function test.

(a) Study drug(s) refers to MLN0128 and MLN1117. If study drug(s) are to be held, then both agents should be held for patients taking both MLN0128 and MLN1117.

6.6.9 Management of Noninfectious Pneumonitis

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

Table 6.m Management of Noninfectious Pneumonitis

Grade	Description	Treatment	Study Drug Dose Modification
1	Asymptomatic: Radiographic findings only.	Rule out infection and closely monitor.	None
2	Symptomatic: Not interfering with activities of daily living.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Interrupt study drug (a) treatment: • When symptoms ≤Grade 1, reinitiate study drug(s) (a) treatment with a 25% dose reduction in the MLN0128. (b) • If no recovery within 4 weeks, then discontinue study drug treatment.
3	Symptomatic: Interfering with activities of daily living; Requires administration of oxygen.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Interrupt study drug (a) treatment until symptoms resolve to ≤Grade 1. • Consider re-initiating MLN0128 treatment with a 25% dose reduction. (b) • If toxicity recurs at Grade 3, discontinue study drug treatment.
4	Life-threatening: Ventilatory support indicated.	Rule out infection and consider treatment with corticosteroids.	Discontinue study drug treatment.

(a) Study drug(s) refers to MLN0128 and MLN1117. If study drug(s) are to be held, then both agents should be held for patients taking both MLN0128 and MLN1117.

(b) As described in Section 6.2, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

6.6.10 Management of Clinical Events: Paclitaxel

For more information on the management of clinical events in patients receiving paclitaxel, refer to the most recent paclitaxel USPI or SmPC.

6.7 Blinding and Unblinding

Not applicable. This is an open-label study.

6.8 Description of Investigational Agents

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

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

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

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

MLN1117 will be supplied as 100 mg capsules for oral administration. Each 100 mg capsule contains 100 mg of MLN1117 and the following inactive ingredients: hard gelatin capsule and small amount of colloidal silicon dioxide.

Refer to the MLN0128, MLN1117, and MLN0128+MLN1117 IBs for full details.

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

6.9 Preparation, Reconstitution, and Dispensation

MLN0128 and MLN1117 dosage forms will be provided in labeled bottles 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 capsules.

6.10 Packaging and Labeling

MLN0128 and MLN1117 will be provided by Millennium and will be handled at the investigative site as open-label material.

MLN0128 will be provided in 30-ct, 60-cc high-density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal. MLN1117 will be provided in 14-ct, 30-cc HDPE bottles with child-resistant caps and induction seal.

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

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

6.11 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN0128 and MLN1117 should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F-86°F). All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All MLN0128 and MLN1117 supplies should be used before the retest expiry 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.

Because MLN0128 and MLN1117 are investigational agents, they should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will receive instructions for home storage and administration of MLN0128 and MLN1117.

Patients will be instructed to return any unused study drug in the original packaging along with their completed diary cards at the appropriate visits.

Paclitaxel should be stored according to instructions provided in the manufacturer's package insert or SmPC.[43,44]

Please refer to the Study Manual for additional instructions.

7. STUDY CONDUCT

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

7.1 Study Personnel and Organizations

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

7.2 Arrangements for Recruitment of Patients

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

7.3 Treatment Group Assignments

A centralized randomization procedure via Interactive Voice/Web Response System (IXRS) will be used to assign treatment. Patients will be randomized strictly sequentially at a center as they become eligible for randomization. Randomization will be stratified by histological subtype, lines of prior chemotherapy, and prior use of taxanes (see Section 8.1.2). If a patient discontinues

from study drug, the randomization code will not be reused, and the patient will not be allowed to re-enter the study.

7.4 Study Procedures

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

7.4.6 Vital Signs

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

7.4.7 Pregnancy Test

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

7.4.8 ECOG Performance Status

The ECOG performance status (refer to Section 14.1) will be assessed at the times specified in the Schedule of Events.

7.4.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from first dose of study drug through 30 days after the last dose of study drug. See Section 6.3 and Section 6.4 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 they have been randomized to a treatment arm. Procedures for completing the enrollment information are described in the Study Manual.

7.4.12 ECG

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

7.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Clinical laboratory evaluations will be performed as outlined below.

Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedule of Events. Results of hematology and clinical chemistry safety labs must be available and reviewed by the investigator before enrollment and initial administration of any study drug. For patients randomized to receive paclitaxel (Arm A and Arm B), results of hematology and chemistry safety laboratory testing must be reviewed by the investigator or appropriate designee before administering paclitaxel.

Hematology

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

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

Coagulation

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

- aPTT.
- PT/international normalized ratio.

Clinical Chemistry

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

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

- Gamma glutamyl transferase
- Sodium
- Amylase
- HbA1c at the times specified in the Schedule of Events
- Protein (total)

Urinalysis

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

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

Fasting Lipid Profile

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

- Cholesterol (total)
- Triglycerides
- High-density lipoprotein cholesterol
- Low-density lipoprotein cholesterol

7.4.14 Fasting Serum Glucose

Fasting serum glucose will be measured in the clinic at the time points specified in the Schedule of Events. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. For patients in Arm A (single-agent paclitaxel), Arm B (paclitaxel+MLN0128), and Arm C (single-agent MLN0128), the sample will be collected predose; after predose blood draws are complete, patients receiving single-agent MLN0128 QW in Arm C should consume a light meal before dosing (Section 6.1). For patients in Arm D (MLN0128+MLN1117), the sample should

be taken approximately 2 hours after study drug administration with the patient continuing to fast until the sample is taken.

7.4.15 Disease Assessment

Patients will undergo CT (with contrast) or MRI (with contrast) as appropriate to monitor and assess disease progression, using RECIST guidelines (version 1.1), where measurable disease is defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded).[41] Each lesion must be ≥10 mm in long axis when measured by CT, MRI, or caliper measurement by clinical exam. Lymph nodes must be ≥15 mm in short axis when measured by CT or MRI. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Anatomical measurements will be collected at Baseline and at each subsequent evaluation for each target lesion, using an imaging modality consistent with the one 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.

All images will be collected and quality controlled by a sponsor-specified central imaging vendor. Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents.

7.4.16 Tumor Biopsies and Archival Tumor Samples

Fresh tumor biopsies and archival tumor samples (banked formalin-fixed, paraffin-embedded tumor tissue) should be obtained at Screening. The reason for requiring both archival and fresh tumor biopsies is to understand the changes that occur from archival tissue to second-line or third-line therapy. These baseline tumor samples will be used for assessment of candidate biomarkers predictive of response to single-agent and combination treatment, including but not limited to PTEN, PIK3CA, mTOR, KRAS, and microsatellite instability. In addition, fresh tumor biopsy samples will also be obtained on Cycle 1 Day 22 for subjects enrolled in Arm C and Arm D to identify adaptive response mechanisms to treatment of MLN0128 or MLN0128+MLN1117.

Fresh tumor biopsies will be obtained as indicated in the Schedule of Events. The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically, if appropriate.

Detailed instructions for the collection, processing, and shipment of the fresh and archival tumor biopsy samples are provided in the Study Manual.

7.4.17 PK Measurements (Arms B, C, and D only)

PK samples collected in this study will be used to quantify MLN0128 and MLN1117. Patients must note in dosing diaries the dates and times when they take their doses of MLN0128 and/or MLN1117 before the days when the clinical visits for PK sampling are scheduled. These dates and times will be noted in the eCRF. Blood samples will be collected at the time points specified in the Pharmacokinetic Sample Breakdown table.

PK data collected in this study is for population PK analysis only and may be combined with similar data from other clinical studies of MLN0128 and MLN1117. The results of such analyses will be reported at a later point in a separate population PK report and will not be part of the clinical study report for this study.

7.4.18 QOL Assessment

The QOL instruments, EORTC QLQ-C30 and EORTC QLQ-EN24, will be administered as specified in the Schedule of Events and must be completed before other assessments are performed or study drug is administered.

The EORTC QLQ-C30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The time recall period for this instrument is 1 week (the past week). It is a reliable and valid measure of health-related QOL in patients with cancer and takes about 11 minutes to administer. The instrument consists of a brief (30-item) questionnaire that has been validated and used in many countries.

The EORTC QLQ-EN24 endometrial cancer module (24-items) has 13 domains: lymphedema, urologic problems, gastro-intestinal problems, body image, sexual/vaginal problems, back/pelvic pain, tingling/numbness, muscular/joint pain, hair loss, taste change, sexual interest, sexual activity, and sexual enjoyment (disease symptoms and side-effects of treatment). It has been validated in patients with endometrial cancer and is available in multiple languages.

7.4.19 DNA Measurements

CCI

[redacted]

7.5 Completion of Treatment

Patients will be considered to have completed treatment if they discontinue treatment with study drug for any of the reasons outlined in Section 7.7.

The maximum duration of treatment for patients will be 24 months unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued treatment beyond 24 months.

7.6 Completion of Study

Patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section 7.8.

7.7 Discontinuation of Treatment With Study Drug

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

- AE.

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

Patients must discontinue study drug if they experience disease progression or unacceptable toxicity, or if they become pregnant.

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

Note that some patients may discontinue study drug for reasons other than progressive disease. Up until Amendment 06, after EOT, these patients were to remain in the study for posttreatment assessments of PFS and OS, during the posttreatment follow-up period.

7.8 Withdrawal of Patients From Study

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

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by subject.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

7.9 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 study drug 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 study drug 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

Summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data.

A formal statistical analysis plan (SAP) will be developed and finalized before database lock. The SAP will outline all data handling conventions and specify all statistical methods to be used for safety and efficacy data analysis. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the clinical study report.

8.1.1 Determination of Sample Size

The primary efficacy endpoint of the study is PFS and the primary comparison is between the paclitaxel and the paclitaxel+MLN0128 4 mg QD×3 treatment arm. Assuming the median PFS is 4 months for paclitaxel and paclitaxel+MLN0128 4 mg QD×3 can improve the median to 6.5 months (hazard ratio of 0.615, approximately 38% reduction in the hazard rate) a total of 134 PFS events and 90 patients per treatment arm are required. The calculations are based on a power of 80%, 2-sided alpha of 5%, and a dropout rate of 15% due to lost to follow-up or withdrawal of consent. Enrollment to the third treatment arm of single-agent MLN0128 30 mg QW and the fourth treatment arm of MLN0128 4 mg QD×3 in combination with 200 mg

MLN1117 has been closed. The total sample size for the study will be approximately 242 patients.

The total accrual duration will be approximately 25 months to complete enrollment in the paclitaxel and paclitaxel+MLN0128 4 mg QD×3 treatment arms. The final analysis for the primary comparison of PFS between the paclitaxel treatment arm and the paclitaxel+MLN0128 4 mg QD×3 treatment arm will occur approximately 5 months after the last patient is randomized.

8.1.2 Randomization and Stratification

Patients will be randomized in a 1:1:1:1 ratio to the 4 treatment arms:

- Arm A: Weekly paclitaxel.
- Arm B: Weekly paclitaxel+MLN0128 4 mg QD×3.
- Arm C: MLN0128 30 mg QW.
- Arm D: MLN0128 4 mg+MLN1117 200 mg QD×3.

In the event that enrollment into a treatment arm(s) is closed, patients will be randomized 1:1 into the remaining treatment arms. A centralized randomization using IXRS will be used with the following stratification factors:

- Histological subtype: endometrioid vs nonendometrioid.
- Line(s) of prior chemotherapy: 1 vs 2.
- Prior taxane therapy (other than weekly): yes vs no.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Intent-to-treat (ITT) population: patients who are randomized will be used for analysis of PFS, TTP, and OS.

- Safety population: patients who receive at least 1 dose of study drug will be used for all safety analyses.

- 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.

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 by treatment arm, including gender, age, race, weight, height, and other appropriate baseline characteristics. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

The primary endpoint for the study is PFS, defined as the time from the date of randomization to the date of first documentation of progression or death due to any cause, whichever occurs first. For a patient who has not progressed and is last known to be alive, PFS will be censored at the last response assessment that is SD or better. The primary efficacy analysis will be based on the ITT population.

The Kaplan-Meier method will be used to analyze the distribution of PFS for each treatment arm, as outlined in the study objectives. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles along with associated 2-sided 95% CIs, hazard ratio along with associated 95% CI, and Kaplan-Meier estimates at relevant time points will be presented. The p-value from a stratified log-rank test will be presented for the primary comparison of paclitaxel and paclitaxel+MLN0128 and the secondary objective comparing paclitaxel to both single-agent

MLN0128 and MLN0128+MLN1117. The primary hypothesis is to be tested at the 0.05 significance level (2-sided).

Secondary efficacy endpoints include OS, ORR, TTP, and CBR (CR+PR+SD).

OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed using similar methods as the primary endpoint of PFS.

ORR is defined as the proportion of patients who achieve a best response of CR or PR. CBR is defined as the proportion of patients who achieve a best response of CR, PR, or SD. A stratified Cochran-Mantel-Haenszel test will be used to compare ORR and CBR between treatment arms. The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented.

TTP is defined as the time from the date of randomization to the date of first documentation of progression. For a patient who has not progressed, TTP will be censored at the last response assessment that is SD or better. TTP will be analyzed using similar methods as the primary endpoint of PFS.

Duration of SD is defined as the time from the date of randomization to the date of first documentation of disease progression for patients who achieved SD as the best overall response.

Sensitivity analyses for time-to-event endpoints (PFS, TTP) and response endpoints (ORR and CBR) may be performed based on results from the central imaging vendor.

8.1.7 Analyses of Patient-Reported Outcomes

Patient-reported outcome (PRO) assessments using the EORTC QLQ-C30 and EORTC QLQ-EN24 questionnaires will be analyzed to determine if response to therapy and side effects of therapy are accompanied by measurable changes in the PROs. Published scoring manual and guidelines will be used to score EORTC QLQ-C30 and EORTC QLQ-EN24 scale scores and handle missing data.

Descriptive statistics for baseline values, actual values, and the change from Baseline will be presented at each scheduled time point for each of the functional and symptom scores, and the global health status/QOL score from the EORTC QLQ-C30 questionnaire and the thirteen symptoms scales from the EORTC QLQ-EN24 questionnaire. Differences between treatment

arms in the EORTC QLQ-C30 and EORTC QLQ-EN24 scores will be evaluated. Longitudinal analysis of PRO scores will be performed using linear mixed models.

8.1.8 PK/Pharmacodynamics/Biomarkers

PK Analysis

Individual plasma concentration-time data will be reported in a by-patient listing. The PK and pharmacogenetic data collected in this study are intended to contribute to future population PK analysis. These data may be combined with data from other studies in which the PK of MLN0128 or MLN1117 is characterized for population PK analysis. The analysis plan for the population PK analysis will be separately defined and the results of these analyses will be reported in a separate population PK report.

Biomarkers

CCI

[redacted]

8.1.9 Safety Analysis

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

TEAEs 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.

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

- TEAEs.

- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- SAEs.

The most commonly reported TEAEs (ie, those events reported by ≥10% of patients in each treatment arm) will be tabulated by the MedDRA preferred term. A listing of deaths within 30 days of last dose of study drug and TEAEs resulting in study drug discontinuation will be provided.

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

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

Concomitant medications will be tabulated by World Health Organization drug dictionary generic term.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN0128 in combination with paclitaxel, MLN0128+MLN1117, or single-agent MLN0128.

ECG Analysis

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

8.1.10 Interim Analysis

There will be 2 interim analyses with early stopping rules for futility in both the single-agent MLN0128 and MLN0128+MLN1117 arms using the Bayesian predictive probability design.[45] The endpoint for the interim analysis will be based on the number of patients who achieve CR or PR of any duration, or SD ≥16 weeks as assessed by the investigator (clinical benefit at 16 weeks). The decision rule for the interim analyses is derived based on the following assumptions:

- Ineffective CBR-16 rate (Ho): 30%.
- Effective CBR-16 rate (Ha): 50%.
- Alpha=10%; power=80%.
- Prior Beta Distribution Parameters: α_0=0.30, β_0=0.70.
- The probability of early termination under the null hypothesis is 77%.

Each interim analysis will be based on patients who have had the opportunity to complete a minimum of 4 cycles or have discontinued study drug before the end of Cycle 4. Based on the first 20 patients in each arm, 1 or both arms may be dropped if at most 6 patients experience clinical benefit at 16 weeks in each arm. After the first 30 patients in each arm have been evaluated following 4 cycles of treatment, 1 or both arms may be dropped if at most 10 patients experience clinical benefit at 16 weeks in each arm.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Pretreatment Event Definition

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

9.1.2 AE Definition

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

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

9.1.3 SAE 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 one 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.[42] Clarification should be made between a 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 WBC 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 AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 9.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 9.1) must be reported (see Section 9.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE

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

SAE Reporting Contact Information

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010.[42] 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 AEs and Period of Observation

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

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

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the 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.

10. ADMINISTRATIVE REQUIREMENTS

10.1 GCP

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 randomized subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

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

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

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

10.4 Study Monitoring

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

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

requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

10.5 Ethical Considerations

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

10.6 Patient Information and Informed Consent

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

10.7 Patient Confidentiality

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

10.8 Investigator Compliance

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

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

10.9 On-site Audits

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

10.10 Investigator and Site Responsibility for Drug Accountability

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

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

10.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the Medical Information Call Center/CCI and report the complaint. The contact information is as follows:

Medical Information Center: CCI
Phone:
Fax:
Email:
Hours:

Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to [redacted] (refer to Section 9.2).

10.12 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 calendar days for fatal and life-threatening events and 15 calendar days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.13 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.

10.14 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 and 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 and 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.

11.1 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

11.2 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

12. INVESTIGATOR AGREEMENT

I have read Protocol C31004 Amendment 05: A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer.

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice, the ethical principles that have their origin in the last version of the Declaration of Helsinki, 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)

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14. APPENDICES

14.1 Eastern Cooperative Oncology Group (ECOG) 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, et al. 1982.[46]

14.2 Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (a):
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation (a):
  - Oral.
  - Injectable.
  - Implantable (b).
- Intrauterine device (IUD) (b).
- Intrauterine hormone-releasing system (IUS) (b).
- Bilateral tubal occlusion (b).
- Vasectomized partner (b) (c).
- Sexual abstinence (d).

Methods that are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide (e).
- Cap, diaphragm, or sponge with spermicide (e).

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

(a) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

(b) Contraception methods that in the context of this guidance are considered to have low user dependency.

(c) Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomized partner has received medical assessment of the surgical success.

(d) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

(e) A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

14.3 Cockcroft-Gault Equation

For women only:

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

OR

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[47]

14.4 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.[48]

14.5 List of Relevant CYP Inhibitors and Inducers

Moderate CYP1A2 Inhibitors		
Cimetidine	Mexiletine	Oral contraceptives
Methoxsalen		
Strong CYP1A2 Inhibitors		
Fluvoxamine	Ciprofloxacin	Enoxacin
Zafirlukast		
Clinically Significant Enzyme Inducers (Moderate [a] CYP1A2 and Strong CYP3A4)		
Phenytoin	Rifampin	Ritonavir
Teriflunomide	Carbamazepine	Enzalutamide
Mitotane	St. John's wort	

Source: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractions Labeling/ucm093664.htm#table3-2.

Note: This list is not meant to be exhaustive. Please refer to the above link for further information and examples of other CYP inhibitors/inducers.

(a) There are no known strong inducers of CYP1A2 at this time.

14.6 List of BCRP, OCT1, and OCT2 Substrates

BCRP, OCT1, and OCT2 Substrates

BCRP Substrates	OCT1 and OCT2 Substrates
Methotrexate	Metformin
Imatinib	Cimetidine
Topotecan	Amantadine
Lapatinib	Famotidine
Rosuvastatin	Pindolol

14.7 Rationale for Amendment 01

The primary purposes of this amendment are to revise dosing regimens for MLN0128, increase the maximum dose reductions from 2 to 3 for MLN0128, and clarify management of treatment-emergent adverse events. In addition, this amendment reduces the cardiac monitoring requirements based on results of a dedicated QT study (Study C31002), which indicated that treatment with MLN0128 is not associated with clinically meaningful effects on the overall electrocardiographic safety profile.

Purposes for Amendment 01

The purposes of this amendment are:

- Added EudraCT number and Millennium corporate identification to Title Page.
- Study Overview Diagram: Clarified description of which groups will continue treatment until disease progression, toxicity, or withdrawal of consent.
- Schedule of Events: Changed general study visit window to align with other phase 2 protocols (allow ±2 day window for holidays, vacations, or other administrative reasons after Cycle 2 Day 1, without permission from the medical monitor).
- Schedule of Events: Removed Screening ECHO/MUGA.
- Schedule of Events: Aligned ECG collection with other phase 2 protocols (Screening, Day 1 of every cycle, and EOT).
- Schedule of Events: Increased pregnancy testing requirements for women of childbearing potential to every cycle.
- Schedule of Events: Aligned fasting lipid profile collection with other phase 2 protocols (Screening, Day 1 of every cycle starting with Cycle 2, and EOT) and removed the requirement to collect the Screening sample within 14 days before Cycle 1 Day 1.
- Schedule of Events: Aligned HbA1c testing with other phase 2 protocols, including changing from Day 15 to Day 1 and decreasing from every 2 cycles to every 3 cycles in Cycles 1 through 8.
- Schedule of Events: CCI [redacted]
- Schedule of Events: Added a visit window for PFS and OS follow up.
- Schedule of Events: Added footnote k, providing window for time from randomization to first dose of study drug.
- Schedule of Events: Clarified footnote l regarding requirements for safety laboratory results to be reviewed relative to first dose and, for patients receiving paclitaxel, before each paclitaxel dose.
- Schedule of Events: Clarified footnote p regarding fasting requirements relative to fasting serum glucose sample collection and added instructions for the fasting serum glucose sample to be collected predose for patients receiving paclitaxel.

- Section 1.2.1 and Section 1.3.1: Added alternative names for MLN0128 and MLN1117.
- Section 1.4: Added rationale for proposed doses and schedules in paclitaxel + MLN0128, single-agent MLN0128, and MLN0128 + MLN1117 treatment arms.
- Section 4.1: Decreased the dose of MLN0128 in Arms B and D from 8 mg to 4 mg.
- Section 4.1: Clarified treatment days for single-agent MLN0128 treatment arm (Arm C).
- Section 4.1: Clarified description of PFS follow up visits.
- Section 4.1: Clarified timing of tumor sampling.
- Section 4.2: Clarified definition of enrollment and updated number of study sites.
- Section 4.3: Clarified criteria for closing the study.
- Section 5.1: Clarified Inclusion Criterion 1 regarding endometrial cancer confirmation and requirements for eligibility.
- Section 5.1: Clarified Inclusion Criterion 8 regarding use of contraception by female patients.
- Section 5.1: Deleted Inclusion Criterion 9 regarding LVEF as measured by ECHO or MUGA during Screening.
- Section 5.2: Clarified description of previous taxane treatment in Exclusion Criterion 1.
- Section 5.2: Deleted Exclusion Criterion 6 regarding anticoagulant therapy.
- Section 5.2: Revised Exclusion Criterion 13 to consider elevation of either systolic or diastolic blood pressure hypertension.
- Section 6.1: Clarified instructions for study drug administration.
- Section 6.2: Added the combination of MLN0128+MLN117 for the investigator to consider when assessing whether an AE is possibly related to study drug.
- Section 6.2: Revised maximum dose reductions from 2 to 3 for MLN0128.
- Table 6-1: Revised paclitaxel dose reduction guidelines.
- Table 6-2: Revised dose reduction schedule for MLN0128.
- Section 6.3: Clarified description of excluded concomitant medications and procedures.
- Section 6.5.1: Added instruction to avoid exposure to live vaccines.
- Section 6.5.1: Added instruction to drink fluids to prevent dehydration.
- Section 6.5.2: Clarified heading to include both single-agent paclitaxel and paclitaxel + MLN0128 treatment arms.
- Section 6.6.1: Clarified instructions for management of hyperglycemia.
- Table 6-3: Clarified instructions for dose reductions for management of clinical events to include only reductions in MLN0128.
- Table 6-6: Clarified instructions for management of rash.
- Section 6.6.6: Clarified instructions for management of QTc prolongation.
- Table 6-10: Clarified dose modification instructions for Grade 2 toxicity.

- Table 6-11: Deleted instruction on dose reduction for MLN1117 for ALT/AST elevations.
- Section 7.4.9: Revised period for collection of concomitant medications and procedures to begin at first dose of study drug.
- Section 7.4.13: Aligned clinical laboratory terminology with other phase 2 protocols and added protein to chemistry testing.
- Section 7.4.15: Revised instructions for in-home daily fasting glucose monitoring.
- Section 7.4.16: Added MRI as an optional method of disease assessment.
- Section 7.4.17: Revised description of tumor biopsy assessments.
- Section 7.4.18: Clarified that PK samples will be collected from patients in Arms B, C, and D only.
- Section 7.7: Added instruction for patients to discontinue study drug(s) if they experience disease progression or unacceptable toxicity, or if they become pregnant.
- Section 7.10: Clarified description of duration of follow-up assessments.
- Section 8.1.2: Clarified description of randomization and stratification.
- Section 8.1.6: Added description of secondary efficacy endpoint comparison.
- Section 10.3: Revised requirement for completed eCRFs to include only randomized subjects.
- Section 10.11: Updated Product Complaint contact information.
- Section 10.12: Added description of suspected unexpected serious adverse events reporting.
- Section 11: Added new sections on clinical trial registration and clinical trial results disclosure.
- Section 14.2: Added appendix describing options for acceptable methods of contraception.
- Corrected typographical errors, internal inconsistencies, punctuation, grammar, and formatting.

14.8 Rationale for Amendment 02

The primary purposes of this amendment are to revise the study population for Study C31004 to exclude patients with a known severe hypersensitivity reaction to prior paclitaxel exposure, to exclude patients with active hepatitis B and hepatitis C infections, and to exclude patients who are lactating and breastfeeding or have a positive serum pregnancy test. In addition, this amendment clarifies language regarding usage of contraception and updates references.

Purposes for Amendment 02

The purposes of this amendment are to:

- Add an exclusion criterion regarding females who are lactating and breastfeeding or have a positive pregnancy test.
- Add an exclusion criterion regarding history of severe hypersensitivity reactions to paclitaxel.
- Add an exclusion criterion regarding hepatitis B and hepatitis C infections.
- Add an exclusion criterion regarding patients with hormone-positive disease who have not received endocrine therapy as part of previous standard therapy.
- Clarify contraception language.
- Add the current Summary of Product Characteristics to references to the United States Prescribing Information for paclitaxel.
- Add >60 msec change from baseline to the description of Grade ≥ 3 rate-corrected QT interval prolongation.
- Add reference to Declaration of Helsinki in the Investigator Agreement.
- Correct typographical errors, punctuation, grammar, and formatting.

14.9 Rationale for Amendment 03

The primary purposes of this amendment are to update the dosing conditions for subjects receiving weekly MLN0128 in Arm C, to update the pharmacokinetic (PK) sampling schedule to reflect the dosing change in Arm C, to clarify the procedures and/or timing for imaging collection and clinical laboratory evaluations, to clarify the MLN0128 and paclitaxel dosing instructions, to update the window for obtaining informed consent, and to update the procedures for reporting drug exposure during pregnancy and birth events.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

Changes in Amendment 03

1. Change the dosing conditions for subjects receiving weekly MLN0128 in Arm C, such that subjects take their doses with a light meal.
2. Add a PK sample collection at 3 to 6 hours postdose on Cycle 1 Day 1 for subjects receiving weekly MLN0128 in Arm C.
3. Clarify that all images will be collected and quality controlled by a sponsor-specified central imaging vendor.
4. Replace references relating to QD or QD×5D dosing with the appropriate dosing instructions.
5. Clarify the procedures for fasting serum glucose monitoring.
6. Clarify that informed consent may be signed more than 28 days before Cycle 1 Day 1.
7. Clarify the dosing instructions for patients receiving paclitaxel in Arm A or Arm B.
8. Update the procedures for reporting drug exposure during pregnancy and birth events.
9. Clarify that all CT and MRI scans should be acquired with IV contrast unless contraindicated for a particular patient.

14.10 Rationale for Amendment 04

This document describes the changes in reference to the protocol incorporating Amendment04. The primary purpose of 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, guidelines for paclitaxel dose modification, list of prohibited concomitant medications, description of potential drug-drug interactions, list of relevant CYP inhibitors, and dietary restrictions related to CYP inhibitors and inducers have been updated accordingly.

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 14.12.

Changes in Amendment 04

1. Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.
2. Clarify the guidelines for paclitaxel dose modification and delay.
3. Update the list of concomitant medications prohibited during the study.
4. Update the description of potential drug-drug interactions in Arm D.
5. Update the list of relevant CYP inhibitors and inducers.
6. Remove dietary restrictions related to CYP inhibitors and inducers.

14.11 Rationale for Amendment 05

This document describes the changes in reference to the protocol incorporating Amendment 05. The primary purpose of this amendment is to update the sample size for the study to reflect changes in study design and the closure of enrollment into Arms C and D. In addition, the amendment updates administrative information and clarifies the specified study procedures, recommendations, or requirements.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

Changes in Amendment 05

7. Update the sample size for the study to reflect changes in study design and the closure of enrollment into Arms C and D.
8. Update the Global Clinical Lead for the study.
9. Clarify the text regarding image collection for disease assessment.
10. Add that sensitivity analyses of efficacy endpoints may be performed.
11. Clarify the instructions for contrast use in tumor evaluation imaging.
12. Clarify that Screening must occur within 28 days of Cycle 1 Day 1.
13. Clarify the timing for considering doses missed in the case of emesis after study medication ingestion.
14. Clarify the guidelines for paclitaxel dose modifications.
15. Update the list of relevant cytochrome P450 inhibitors and inducers.

14.12 Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 06 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Removed long-term follow up (PFS follow up and/or OS follow up) for patients after end of treatment.

The primary change occurs in Section 4.1 Overview of Study Design, Section 4.3 Duration of Study, and Section 7.10 Posttreatment Follow-up Assessments (PFS and OS):

Deleted Text

~~Patients who discontinue study treatment for reasons other than progressive disease will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the End-of-Treatment (EOT) visit, then every 3 months (±1 week) until disease progression, death, or start of another anticancer therapy, whichever occurs first. After disease progression, patients will be followed for OS every 3 months (±1 week).~~

AND

~~After EOT, patients will be followed for PFS and OS. For those patients who discontinue MLN0128 for any reason other than radiographic disease progression, CT (with **contrast**) or MRI scans (with contrast) should be completed to further assess disease progression (per RECIST, version 1.1).[41]~~

AND

~~**7.10 Posttreatment Follow-up Assessments (PFS and OS)**~~

~~After EOT, patients will be followed for PFS and OS. For those patients who discontinue study drug for any reason other than radiographic disease progression, CT (with contrast) or MRI scans (with contrast) should be completed to further assess disease progression (per RECIST, version 1.1) until the occurrence of progression or start of another anticancer therapy.[41] Refer to the Schedule of Events for appropriate assessments during posttreatment follow-up.~~

~~Survivor information may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieved from online or other databases (eg, Social Security indexes). In addition, the start of another anticancer therapy will be collected.~~

~~NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 9 for details regarding definitions, documentation, and reporting of SAEs.~~

Added Text **Up until Amendment 06, after EOT, patients were to be followed for PFS and**

OS, during the Posttreatment follow-up Period.

Rationale for Change:

In July 2019, the study reached its protocol defined data-driven primary endpoint of PFS. After database lock and review of Topline results, it was determined that any emerging data will not change study conclusions in any meaningful way. Therefore, as of Protocol Amendment 6, requirements for long-term follow up (PFS follow up and/or OS follow up) for patients after EOT visit were removed. The study will continue until patients discontinue treatment.

The following sections also contain this change:

- Protocol Summary
- Study Overview Diagram
- Schedule of Events
- Section 7.7 Discontinuation of Treatment With Study Drug

Change 2: Update to the Global Clinical Lead for the study.

The primary change occurs on the Title Page:

Initial wording	PPD
Amended wording:	PPD

Rationale for Change:

This change was made to update the Global Clinical Lead for the study.

Change 3: Removed in-home glucose monitoring.

The primary change occurs in Section 6.6.1 Management of Hyperglycemia, and Section 7.4.15 In-Home Daily Fasting Glucose Monitoring was deleted:

Initial wording	In addition to obtaining fasting serum glucose levels at the clinic visits as outlined in the Schedule of Events, all patients randomized to receive MLN0128 (ie, Arm B, Arm C, or Arm D) will be provided with a glucometer and trained in its use to

monitor their daily predose fasting blood glucose (FBG) levels at home (see Section 7.4.14). The level should be collected daily, predose on dosing days, and at approximately the same time each day. Patients will be instructed to notify the study staff immediately of any abnormal readings (ie, ≥150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no irregularities in the FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgement and approval. Patients will continue to notify the investigator of FBG levels ≥150 mg/dL, and if blood glucose levels are not well controlled, or if they require either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines (Table 6.d) are provided to aid the investigator in initiating antiglycemic therapies.

Amended wording:

6.6.1 Management of Hyperglycemia

~~In addition to ing~~ **F**asting serum glucose levels **will be obtained** at the clinic visits as outlined in the Schedule of Events **and as described in more detail in Section 7.4.14**. ~~all patients randomized to receive MLN0128 (ie, Arm B, Arm C, or Arm D) will be provided with a glucometer and trained in its use to monitor their daily predose fasting blood glucose (FBG) levels at home (see Section 7.4.15). The level should be collected daily, predose on dosing days, and at approximately the same time each day. Patients will be instructed to notify the study staff immediately of any abnormal readings (ie, ≥150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no irregularities in the FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgement and approval. Patients will continue to notify the investigator of FBG levels ≥150 mg/dL, and if blood glucose~~

~~levels are not well controlled, or if they require either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily.~~ To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines (Table 6.d) are provided to aid the investigator in initiating antiglycemic therapies.

Deleted Text

- ~~Monitor home glucometer test results.~~
- ~~FBG levels ≥150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.~~

Deleted Text

~~7.4.15 In-Home Daily Fasting Glucose Monitoring~~

~~In addition to obtaining fasting serum glucose levels at the clinic visits as outlined in the Schedule of Events, all patients randomized to receive MLN0128 (ie, Arm B, Arm C, or Arm D) will be given a glucometer to monitor their daily FBG levels at home on days when fasting glucose is not measured in the clinic. The level should be collected daily, predose on dosing days, and at approximately the same time each day. Before checking their blood glucose levels, patients should fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment). After fasted testing is complete, patients in Arm C should consume a light meal before MLN0128 dosing (Section 6.1).~~

~~On Cycle 1 Day 1, 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 on dosing days) 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, ≥150 mg/dL) 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 FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgement and approval. Patients will continue to notify the investigator of FBG levels that exceed 150 mg/dL and, if blood glucose levels are not well controlled, or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily.~~

~~See also Section 6.6.1.~~

Rationale for Change:

In July 2019, the study reached its protocol defined data-driven primary endpoint of PFS. After review of safety data, it was determined that there was no significant difference in incidence of hyperglycemia between patients in Arm A (paclitaxel) and Arm B (paclitaxel + TAK-228). Therefore, as of amendment 6, requirement for in-home monitoring was removed. Patients will continue to be evaluated for fasting blood sugar as per Schedule of Events.

The following sections also contain this change:

- **Schedule of Events**
- **7.4.14** Fasting Serum Glucose

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	04-Mar-2020 14:05 UTC
	Biostatistics Approval	04-Mar-2020 14:19 UTC
	Pharmacovigilance Approval	13-Mar-2020 14:52 UTC