Title: A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/ HER2 Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant

NCT Number: NCT02049957

Protocol Approve Date: 26 October 2017

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

- Named persons or organizations associated with the study.
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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 C31001 AMENDMENT 6

MLN0128

A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2– Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant

Protocol Number:	C31001
Indication:	Breast cancer
Phase:	1b/2
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2014-001921-34
Therapeutic Area:	Oncology

Protocol History

Original	06 September 2013	Amendment 4	22 October 2015
Amendment 1	16 June 2014	Amendment 5	12 May 2017
Amendment 2	15 September 2014	Amendment 6	26 October 2017
Amendment 3	12 March 2015		

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Approved by:

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

PPD

Rationale for Amendment 6

This document describes the changes in reference to the protocol incorporating Amendment 6. The primary purpose of this amendment is to update sections affected by new nonclinical data for MLN0128 metabolism by specific cytochrome P450 (CYP) isoforms. The study's exclusion criteria, list of prohibited concomitant medications, list of relevant CYP inhibitors, dietary restrictions related to CYP inhibitors and inducers, use of contrast with magnetic resonance imaging (MRI), and the description of potential drug-drug interactions have been updated accordingly.

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 changes are located, see Appendix 14.10.

Changes in Amendment 6

1. Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.
2. Update the list of concomitant medications prohibited during the study.
3. Update the list of relevant CYP inhibitors and inducers.
4. Remove dietary restrictions related to CYP inhibitors and inducers.
5. Clarify language surrounding the use of contrast with MRI.
6. Update the description of potential drug-drug interactions between MLN0128 and exemestane.
7. Update the signature page.

PROTOCOL SUMMARY

Study Title: A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2− Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant

Number of Patients: Approximately 128 patients will be enrolled in this study from approximately 40 study centers in the United States (US), Belgium, and France. A patient will be considered enrolled after receiving the first dose of MLN0128.

Study Objectives:

Primary Objectives

The primary objectives include:

Phase 1b

- To evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

Phase 2

- To evaluate the antitumor activity by clinical benefit rate at 16 weeks (defined as the proportion of patients who achieve complete response [CR] or partial response of any duration, or have stable disease [SD] at 16 weeks) of treatment with MLN0128 in combination with either exemestane or fulvestrant.

Secondary Objectives

- To further evaluate the antitumor activity of MLN0128 in combination with either exemestane or fulvestrant.
- To evaluate the pharmacokinetics (PK) of MLN0128 and exemestane when administered in combination and to evaluate the PK of MLN0128 when administered in combination with fulvestrant.
- To assess the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

Exploratory Objectives

CCI

Overview of Study Design: This is a phase 1b/2 study of the safety and efficacy of MLN0128 (also known as TAK-228) in combination with exemestane or fulvestrant therapy in women with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2–) advanced or metastatic breast cancer that has progressed on treatment with everolimus in combination with exemestane (any country) or fulvestrant (US only). Patients enrolled in this study will be given either exemestane (any country) or fulvestrant (US only) in combination with MLN0128.

In the phase 1b portion of the study, the safety and tolerability of MLN0128 using a capsule formulation based on unmilled (Part 1) and milled (Part 2) active pharmaceutical ingredient (API) in combination with either exemestane or fulvestrant will be evaluated. Patients enrolled in Part 1 will remain on MLN0128 capsules based on unmilled API and will continue to take their MLN0128 doses with a light meal. Patients enrolled into Part 2 will receive MLN0128 capsules containing milled API and will take each MLN0128 dose on an empty stomach. Patients will be enrolled as follows:

Part 1 Patients (Capsules Based on Unmilled API):

MLN0128+Exemestane Safety Cohort: Six patients will receive MLN0128 capsule formulation based on unmilled API (5 mg once daily [QD]) in combination with exemestane (administered per prior therapy for the patient). Steady-state serial PK samples will be collected to quantify both MLN0128 and exemestane to characterize the PK of MLN0128 and exemestane when administered in combination.

MLN0128+Fulvestrant Safety Cohort (US Only): Six patients will receive MLN0128 capsule formulation based on unmilled API (5 mg QD) in combination with high-dose fulvestrant (500 mg intramuscularly every month).

Part 2 Patients (Capsules Based on Milled API):

MLN0128+Exemestane/Fulvestrant Safety Cohort 1: Six patients will receive MLN0128 capsule formulation based on milled API (3 mg QD) in combination with either exemestane (any country) or fulvestrant (US only). Serial blood samples will be collected to evaluate the PK of MLN0128 when administered in combination with either exemestane or fulvestrant. After the last patient completes Cycle 1, a safety and tolerability assessment will be performed. If ≥2 dose-limiting toxicities (DLTs) occur in these 6 patients, the dose of MLN0128 will be reduced to 2 mg QD for patients subsequently enrolled in Cohort 2 of Part 2 of the phase 1b portion of this study. If ≤1 DLT occurs in Cohort 1, the dose of MLN0128 will be escalated to 4 mg QD for patients entering Cohort 2.

MLN0128+Exemestane/Fulvestrant Safety Cohort 2: Six patients will receive MLN0128 capsule formulation based on milled API, either 4 or 2 mg QD based on the safety observed in Cohort 1, in combination with either exemestane (any country) or fulvestrant (US only). Serial PK samples will be collected as outlined for Cohort 1. After the last patient completes Cycle 1, a safety and tolerability assessment will be performed.

- If ≥2 DLTs occur in the treatment group receiving 4 mg of MLN0128, the subsequent phase 2 portion of the study will be initiated at 3 mg of MLN0128 QD in combination with exemestane or fulvestrant.
- If ≤1 DLT occurs in the treatment group (either at 4 mg or 2 mg QD), the subsequent phase 2 portion of the study will be initiated at the same dose (either 2 mg or 4 mg MLN0128 QD) in combination with exemestane or fulvestrant.
- If ≥2 DLTs occur in the treatment group receiving 2 mg of MLN0128 in combination with either exemestane and/or fulvestrant, the study will be stopped.

In the phase 2 portion of the study, patients will be administered MLN0128 capsule formulation based on milled API at 4 mg QD in combination with either exemestane or fulvestrant, based on the outcome of the safety and tolerability analysis performed in the phase 1b portion of the study. Patients will be enrolled into one of 2 parallel cohorts, depending on the quality and/or duration of their prior response to everolimus in combination with either exemestane (any country) or fulvestrant (US only) as follows:

> **Everolimus-Resistant Cohort:** This is a cohort of 56 response-evaluable patients who have progressed on prior treatment with everolimus in combination with either exemestane (any country) or fulvestrant (US only) without achieving an objective response (CR or partial response) or after achieving SD for <6 months as their best response. Patients will receive MLN0128 in combination with exemestane (any country) or fulvestrant (US only).
>
> **Everolimus-Sensitive Cohort**: This is a cohort of 48 response-evaluable patients who have progressed on treatment after achieving a CR or partial response of any duration, or SD ≥6 months with prior everolimus treatment in combination with either exemestane (any country) or fulvestrant (US only). Patients will receive MLN0128 in combination with exemestane (any country) or fulvestrant (US only).

Sparse PK samples will be collected from all patients enrolled in the study (regardless of whether they are administered MLN0128 in combination with exemestane or fulvestrant) for plasma PK analysis of MLN0128 only. 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.

Radiological tumor evaluations will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events. Adverse events will be assessed and clinical laboratory values, vital signs, and electrocardiograms will be obtained to evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

Study Population: Female patients must be 18 years of age or older and postmenopausal for at least 1 year before the Screening visit to be enrolled in the study. Patients must have advanced or metastatic breast cancer, and must have histological or cytological confirmation of ER+/HER2– status. Patients who have a history of treated brain metastasis are eligible for the study provided that there is no sign of disease progression or hemorrhage after treatment, they are off-treatment, and have no ongoing requirement for dexamethasone or antiepileptic drugs. Patients must have an Eastern Cooperative Oncology Group performance status of 0 to 2 and adequate clinical laboratory values and left ventricular ejection fraction. Patients must provide paraffin blocks or a minimum of 10 unstained slides of available archival tumor tissues (paraffin blocks are preferred) or a tumor biopsy before beginning treatment with MLN0128.

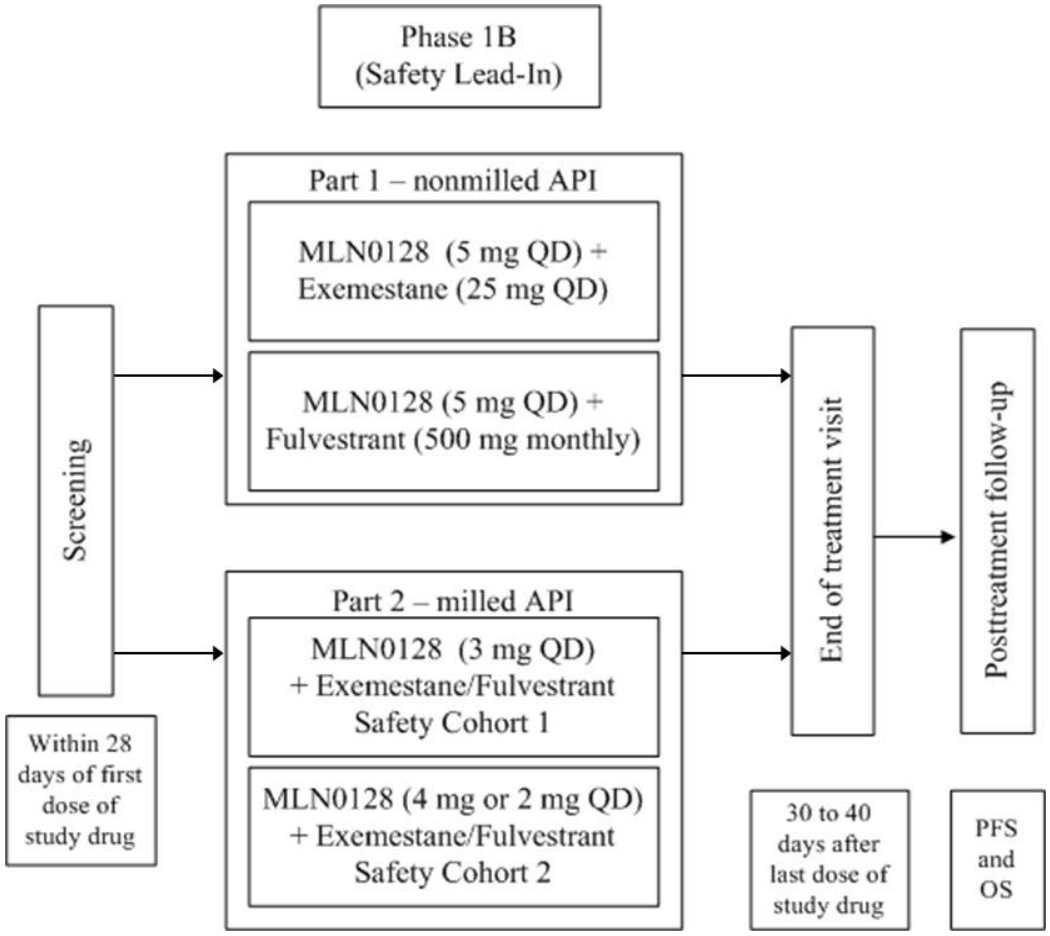
To be enrolled in the phase 1b portion of the study, patients may have SD or disease progression during their most recent treatment with exemestane (any country) or fulvestrant (US only). Exemestane or fulvestrant in combination with MLN0128 can also be initiated as a new line of therapy. To be enrolled in the phase 2 portion of the study, patients must have measureable disease defined as at least 1 extraosseous lesion that can be accurately measured in at least 1 dimension (RECIST, version 1.1) or bone lesions (lytic or mixed [lytic plus sclerotic]) and have had disease progression during treatment with everolimus in combination with either exemestane (any country) or fulvestrant (US only). Treatment with everolimus in combination with either exemestane (any country) or fulvestrant (US only) is not required to be the most recent treatment before enrollment.

Duration of Study: Patients will receive MLN0128 in combination with either exemestane (any country) or fulvestrant (US only) until they experience disease progression. Patients will discontinue treatment if they have an unacceptable drug-related toxicity. The maximum duration of treatment will be 24 months. If after discussion between the investigator and sponsor it is determined that a patient would derive benefit, the patient may continue treatment beyond 24 months.

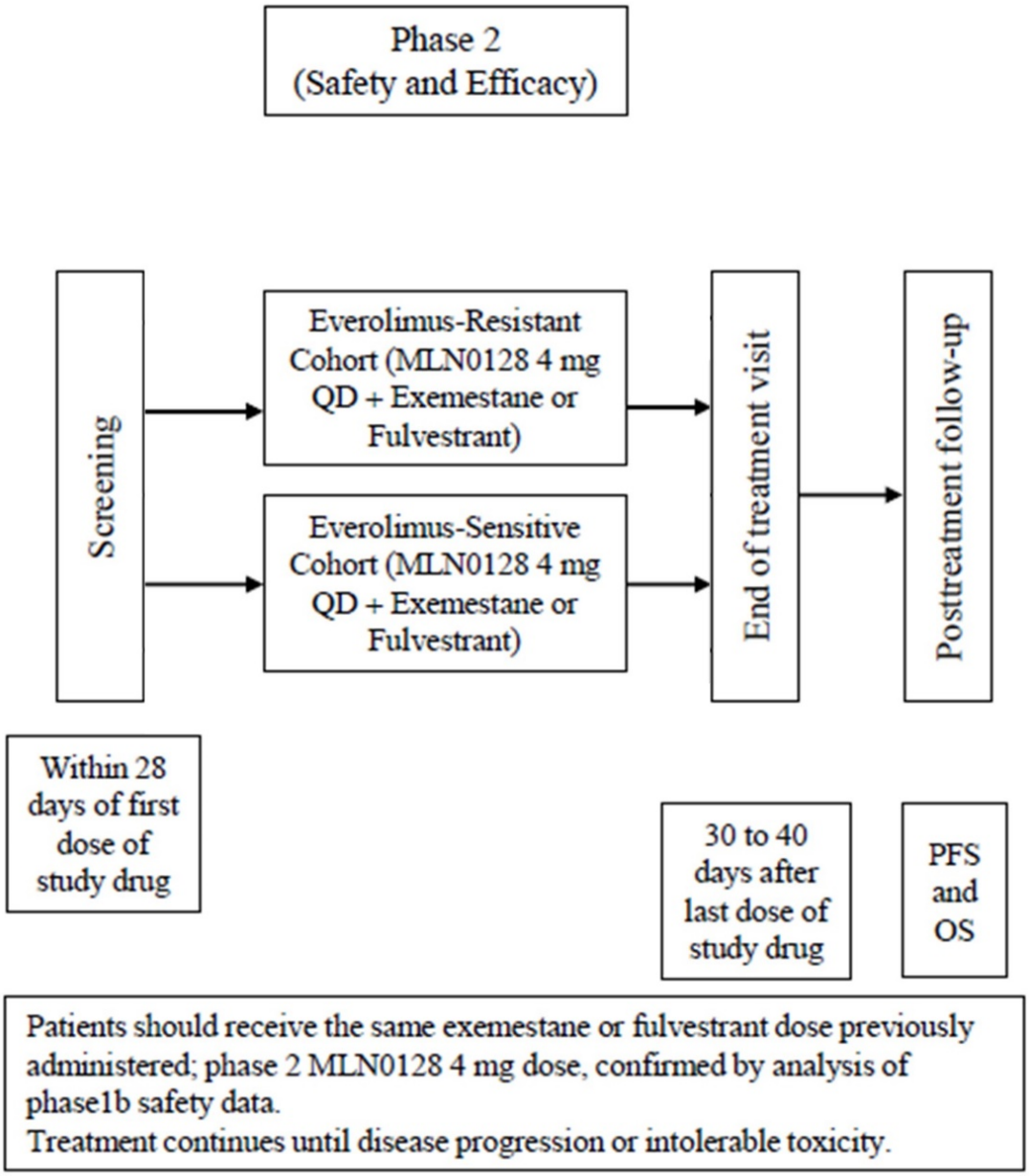
Patients will attend an End-of-Treatment (EOT)/Early Termination visit 30 days after receiving their last dose of MLN0128, or at the start of subsequent anticancer therapy. After EOT, patients will be followed for progression-free survival and overall survival. The study will be terminated 6 months after the last patient completes an EOT study visit.

STUDY OVERVIEW DIAGRAM

Phase 1b (Safety Lead-In)



Phase 2 (Safety and Efficacy)



Phase 1b patients are not eligible for participation in phase 2. In the phase 2 portion, patients will be enrolled into one of 2 parallel cohorts, depending on the quality and/or duration of their prior response to everolimus in combination with either exemestane (any country) or fulvestrant (United States only).

API=active pharmaceutical ingredient, OS=overall survival, PFS=progression-free survival, QD=once daily.

SCHEDULE OF EVENTS

	Screening (a)	TREATMENT CYCLES										EOT/ ET (b)	PFSFU /OSFU
		Cycle 1		Cycle 2			Cycle 3	Cycle 4		Cycles 5 and Beyond			
	Day -28 to Day -1	Day 1	Day 15 (±2 Days)	Day 1	Day 15 (±2 Days)	Day 28 (±2 Days)	Day 1	Day 1	Day 28 (±2 Days)	Day 1	Day 28 (±2 Days)		
Study Procedures													
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history (c)	X												
Height	X												
Weight	X	X	X	X	X		X	X		X		X	
Physical examination	X	X	X	X	X		X	X		X		X	
Vital signs (d)	X	X	X	X	X		X	X		X		X	
ECOG performance status	X	X		X			X	X		X		X	
ECHO/MUGA	X												
Single, 12-lead ECG	X	X (e)	X (e)	X (e)								X	
Radiographic tumor evaluation (f)	X					X			X		X (f)		Q3mo (g)
Follow-up phone calls (OS and subsequent anticancer therapy)													Q3mo (g)
Monitoring of concomitant medications and procedures		Recorded from the first dose of MLN0128 through 30 days following the last dose											
Adverse event reporting		Recorded from the first dose of MLN0128 through 30 days after the last dose											
	Serious adverse events (h) will be reported from signing of the ICF through 30 days after the last dose of MLN0128												
MLN0128 administration		QD dosing (see Section 6.1)											

	Screening (a)	TREATMENT CYCLES										EOT/ ET (b)	PFSFU /OSFU
		Cycle 1		Cycle 2			Cycle 3	Cycle 4		Cycles 5 and Beyond			
	Day -28 to Day -1	Day 1	Day 15 (±2 Days)	Day 1	Day 15 (±2 Days)	Day 28 (±2 Days)	Day 1	Day 1	Day 28 (±2 Days)	Day 1	Day 28 (±2 Days)		
Antihormonal therapy administration		Exemestane orally QD or fulvestrant IM every month (i)											
Samples/Laboratory Assessments													
Hematology/chemistry	X1	X1 (j)	X1	X1	X1		X1	X1		X1		X1	
Urinalysis	X1 (k)	X1 (j)	X1	X1	X1		X1	X1		X1		X1	
Coagulation (PT/INR, aPTT) (l)	X1	X1 (j)	X1	X1	X1		X1	X1		X1		X1	
Fasting serum glucose (m)	X1	X1		X1			X1	X1		X1		X1	
In-home daily fasting glucose monitoring (n)		X											
Fasting lipid profile	X1 (o)			X1			X1	X1		X1		X1	
HbA1c	X1						X1			Q3C			
Blood sample for PK analysis (p)		See the Phase 1b Pharmacokinetic and ECG Sample Breakdown and the Phase 2 Pharmacokinetic and ECG Sample Breakdown table											
CCI [redacted]													
CCI [redacted]													
CCI [redacted]													
CCI [redacted]													

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) with permission from the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician.**

aPTT=activated partial thromboplastin time, C=cycle, CT=computed tomography, CCI [redacted] ECHO=echocardiogram, ECG=electrocardiogram,

	Screening (a)	TREATMENT CYCLES										EOT/ ET (b)	PFSFU /OSFU
		Cycle 1		Cycle 2			Cycle 3	Cycle 4		Cycles 5 and Beyond			
	Day -28 to Day -1	Day 1	Day 15 (±2 Days)	Day 1	Day 15 (±2 Days)	Day 28 (±2 Days)	Day 1	Day 1	Day 28 (±2 Days)	Day 1	Day 28 (±2 Days)		

ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOT=End of Treatment (visit), ET=Early Termination, HbA1c=glycosylated hemoglobin, ICF=informed consent form, IM=intramuscular(ly), INR=international normalized ratio, mo=months, MRI=magnetic resonance imaging, MUGA=multiple gated acquisition (scan), OS=overall survival, OSFU=overall survival follow-up, PFS=progression-free survival, PFSFU=progression-free survival follow-up, PK=pharmacokinetic(s), PT=prothrombin time, Q=every, QD=once daily, RECIST=Response Evaluation Criteria in Solid Tumors, SmPC=Summary of Product Characteristics, USPI=United States Prescribing Information, X#=the number of samples required (eg, 2 samples=X2).

(a) Screening assessments are performed within 28 days before the Cycle 1 Day 1 MLN0128 dose. Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

(b) Patients will attend an EOT/ET visit 30 to 40 days after receiving their last dose of MLN0128 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/ET visit should be conducted before the initiation of subsequent anticancer therapy.

(c) For patients enrolling into phase 2 who have measurable disease and are undergoing CT scans (rather than MRIs) for tumor assessment, the most recent CT scan performed before the baseline CT scan for this study will be collected, if available. See Section 7.4.3.

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

(e) Single, 12-lead ECGs will be collected according to the schedule presented in the Phase 1b Pharmacokinetic and ECG Sample Breakdown and the Phase 2 Pharmacokinetic and ECG Sample Breakdown table. When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first.

(f) Contrast-enhanced imaging CT or MRI of the chest, abdomen, and pelvis must be obtained at baseline within 4 weeks before the first dose of MLN0128. Unless contraindicated, such contrast-enhanced imaging CT or MRI scans will be obtained every 2 cycles from Cycle 2 through Cycle 6 (ie, Cycle 2 Day 28, Cycle 4 Day 28, and Cycle 6 Day 28) and then every 3 cycles thereafter (ie, Cycle 9 Day 28, Cycle 12 Day 28, Cycle 15 Day 28, etc). A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all patients with a complete or partial response. For those patients who have documented radiographic disease progression, CT or MRI scans are not required at the EOT visit. The same imaging modality (CT or MRI) should be used throughout the study.

(g) After EOT, patients will be followed for PFS and OS; see Section 7.10 for more details. For those patients who discontinue MLN0128 for any reason other than radiographic disease progression, contrast-enhanced imaging CT or MRI scans should be completed to further assess disease progression (per RECIST, version 1.1).

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

(i) Exemestane or fulvestrant should be administered according to the USPI or SmPC and according to the dose administered during previous treatment.

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

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

(l) Coagulation assessment is required for all patients at times specified in the Schedule of Events. When a tumor biopsy is required, coagulation assessment is required within 24 hours before obtaining the tumor biopsy. See Section 7.4.19 for additional information regarding tumor biopsy.

(m) 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

	Screening (a)	TREATMENT CYCLES										EOT/ ET (b)	PFSFU /OSFU
		Cycle 1		Cycle 2			Cycle 3	Cycle 4		Cycles 5 and Beyond			
	Day -28 to Day -1	Day 1	Day 15 (±2 Days)	Day 1	Day 15 (±2 Days)	Day 28 (±2 Days)	Day 1	Day 1	Day 28 (±2 Days)	Day 1	Day 28 (±2 Days)		

minimum of 8 hours before the assessment) for each of these measurements. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.

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

(o) To be completed within 14 days of Cycle 1 Day 1 dosing.

(p) Blood samples for PK analysis will be performed according to the schedule presented in the Phase 1b Pharmacokinetic and ECG Sample Breakdown and the Phase 2 Pharmacokinetic and ECG Sample Breakdown table.

(q) CCI [redacted]

(r) CCI [redacted]

(s) CCI [redacted]

PHASE 1B PHARMACOKINETIC AND ECG SAMPLE BREAKDOWN

	Phase 1B Patients (Parts 1 and 2)				
	Cycle 1			Cycle 2	
	Day 1	Day 15		Day 1	
	Single, 12-Lead ECG (a)	Single, 12-Lead ECG (a)	PK (MLN0128+Exemestane Safety Cohort and All Part 2 patients)	Single, 12-Lead ECG (a)	PK
Pre-MLN0128 dose (within 0.5 hours before dosing	X	X	X1	X	X1
0.5 hours post-MLN0128 dose (±10 min)			X1		X1
1 hour post-MLN0128 dose (±10 min)			X1		X1
2 hours post-MLN0128 dose (±30 min)	X	X	X1	X	X1
4 hours post-MLN0128 dose (±30 min)	X		X1		X1
8 hours post-MLN0128 dose (±45 min)			X1		

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

Refer to Section 7.4.18 for details regarding the number of patients required from each cohort where blood samples for PK analyses should be obtained.

(a) ECGs are assessed for all patients enrolled in the study. When the timing of an ECG coincides with blood samples for PK analysis, the ECG should be completed first.

PHASE 2 PHARMACOKINETIC AND ECG SAMPLE BREAKDOWN

	Phase 2				
	Cycle 1			Cycle 2	
	Day 1	Day 15		Day 1	Day 15
	Single, 12-Lead ECG (a)	Single, 12-Lead ECG (a)	PK	Single, 12-Lead ECG (a)	PK (b)
At time of scheduled visit					X
Pre-MLN0128 dose (within 0.5 hours before dosing)	X	X		X	
2 hours post-MLN0128 dose (±30 min)	X	X	X	X	
1 hour after previous PK sample					X

ECG=electrocardiogram, PK=pharmacokinetic.

Refer to Section 7.4.18 for details regarding the number of patients required from each cohort where blood samples for PK analyses should be obtained.

(a) ECGs are assessed for all patients enrolled in the study. When the timing of an ECG coincides with blood samples for PK analysis, the ECG should be completed first.

(b) On Cycle 2 Day 15, all patients should take their MLN0128 dose at home before arriving at the clinic for the scheduled visit. All dates and times of the doses taken at home must be recorded on the patient diary card. The first Cycle 2 Day 15 PK sample may be collected at any time during the clinic visit, and a second PK sample will be collected 1 hour after the first PK sample.

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
AI	aromatase inhibitors
AKT	serine/threonine-specific protein kinase (also known as protein kinase B)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
ASCO	American Society of Clinical Oncology
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_t	area under the plasma concentration versus time curve from zero to the last measurable concentration
BOLERO-2	Breast Cancer Trials of Oral Everolimus-2
CBR	clinical benefit rate
CBR-16	clinical benefit rate at 16 weeks
CBR-24	clinical benefit rate at 24 weeks
C_{max}	single-dose maximum (peak) concentration
CAP	College of American Pathologists
CR	complete response
CT	computed tomography
CTC	circulating tumor cell
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment (visit)

Abbreviation	Term
ER	estrogen receptor
ER+/HER2−	estrogen receptor positive/human epidermal growth factor receptor-2 negative
FBG	fasting blood glucose
GCP	Good Clinical Practice
GI	gastrointestinal
HbA1c	glycosylated hemoglobin
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor-2
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF1R	insulin-like growth factor 1 receptor
IM	intramuscular; intramuscularly
IRB	institutional review board
IV	intravenous; intravenously
LVEF	left ventricular ejection fraction
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MLN0128	also known as TAK-228
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian (or mechanistic) target of rapamycin
MUGA	multiple gated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
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)
PPI	proton pump inhibitor
PR	progesterone receptor
PTEN	phosphatase and tensin homolog
PT/INR	prothrombin time/international normalized ratio

Abbreviation	Term
QD	*quaque die*; each day; once daily
QTc	rate-corrected QT interval (msec) of electrocardiograph
RECIST	Response Evaluation Criteria in Solid Tumors
S473	serine 473
S6K	ribosomal protein S6 kinase
SAE	serious adverse event
SD	stable disease
SERD	selective estrogen receptor down regulator
SLD	sum of the longest diameter
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal disposition half-life
TAK-228	MLN0128
TAMRAD	tamoxifen plus everolimus
TEAE	treatment-emergent adverse event
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
TORC1	mammalian (or mechanistic) target of rapamycin complex 1
TORC2	mammalian (or mechanistic) target of rapamycin complex 2
ULN	upper limit of the normal range
US	United States
USPI	United States Prescribing Information
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Epidemiology

Breast cancer is the most frequent cancer diagnosis in women and is the leading cause of cancer-related deaths in women in Europe and the second leading cause of cancer-related deaths in women in the United States (US).[1,2] The American Cancer Society estimates that approximately 232,340 women will receive a new diagnosis of breast cancer in this year. Approximately 39,620 women in the US and 88,886 women in Europe are predicted to die from their disease in 2013.[1,2]

Breast cancer is a heterogeneous disease with different histologies, prognoses, natural history, responses to treatment, and molecular characteristics.[3-5] Breast cancer can be classified into 3 major categories or subtypes: hormone receptor-positive tumors that express estrogen or progesterone receptors (PRs) or both; tumors that over-express the receptor for human epidermal growth factor receptor-2 (HER2); and basal epithelial-like or "triple-negative tumors" that do not express hormone receptors or HER2.[3,6] The hormone receptor-positive tumors, which represent 66% to 75% of breast cancer tumors, consist of 2 main subtypes: luminal A and luminal B.[3,5,7-9]

Antiestrogen Treatment

Antiestrogen therapy remains the first line of therapy for estrogen receptor (ER)-positive tumors both in the adjuvant and metastatic disease settings.[10] Standard antiestrogen therapy for postmenopausal women with hormone receptor-positive metastatic breast cancer involves the sequential use of selective ER modulators (eg, tamoxifen), nonsteroidal or steroidal aromatase inhibitors (AIs), and selective ER down regulators (SERDs; eg, fulvestrant).[9] In the first-line metastatic disease setting, antiestrogen therapy in postmenopausal women may be either monotherapy with a third-generation, nonsteroidal AI (anastrozole or letrozole) or the steroidal AI exemestane or sequential therapy with tamoxifen followed by a third-generation AI.[11,12]

Resistance to antiestrogen treatment occurs commonly in patients and is an important therapeutic limitation. Approximately 30% of patients with metastatic disease have primary resistance to initial endocrine therapy and develop progressive disease within 6 months after initiation of antiestrogen therapy.[9,13] Many other patients may initially respond to

hormonal therapy but then develop secondary resistance defined as progressive disease occurring more than 6 months after initiation of antiestrogen therapy.[9,13] The resistant tumors have not completely lost estrogen dependence and may respond to an additional or alternative antiestrogen therapy, such as the SERD fulvestrant, which binds irreversibly to the ER, leading to receptor blockade and degradation.[14,15] However, the duration of response or remission after subsequent, alternative therapy is often shorter than that achieved with earlier therapy.[15] This suggests that during estrogen deprivation, adaptive changes occur in tumor cells that allow them to proliferate and survive in a low-estrogen environment.

Estrogen Action and Resistance

Several mechanisms may lead to endocrine resistance, but evidence from studies of estrogen action and cell signaling in breast cancer cells indicates that crosstalk between the phosphoinositide 3-kinase (PI3K)/serine/threonine-specific protein kinase (AKT)/mammalian (or mechanistic) target of rapamycin (mTOR) pathway and the ER is an important potential mechanism of resistance to hormone therapy in ER-positive breast cancer. In the classical ligand-dependent genomic action of the ER, estrogen binding to the ERs leads to receptor dimerization that forms a complex with coactivators or corepressors that then binds to estrogen response elements in the promoter region of estrogen responsive genes with subsequent enhancement or repression of transcription.[15,16] However, ERs can be activated via ligand-independent genomic mechanisms that can contribute to endocrine resistance by inducing estrogen-independent growth. Ligand-independent, genomic activation of the ER is mediated through growth factor receptor signaling, such as epidermal growth factor and insulin-like growth factor 1 receptors (IGF1Rs), and subsequent up-regulation of the PI3K/AKT/mTOR signaling pathway. Activated PI3K/AKT/mTOR signaling ultimately leads to phosphorylation of the ER. The phosphorylated ER binds, even in the absence of its physiological ligand, to estrogen-responsive DNA elements to modulate estrogen-responsive target genes inducing proliferation and survival of tumor cells independent of estrogen.[15,17] These data suggest that activation of the PI3K/AKT/mTOR pathway is critical to induce estrogen-independent tumor growth and resistance to antihormonal treatment in breast cancer.

Growth factor and PI3K/AKT/mTOR signaling is often dysregulated in ER+ breast tumors. Approximately 28% to 47% of luminal tumors harbor activating mutations of phosphoinositide 3-kinase, catalytic alpha polypeptide (PIK3CA), and 41% to 48% have activation mutations consisting of the amplification of the IGF1R.[18] Cells in which the

PI3K/AKT/mTOR signaling pathway is activated can proliferate and survive in a low-estrogen environment and are likely to become resistant to estrogen deprivation therapy. Thus, several lines of evidence indicate that PI3K/AKT/mTOR signaling has a central role in paths leading to endocrine resistance. This strongly suggests that inhibitors of the PI3K/AKT/mTOR pathway would have the potential to restore endocrine sensitivity in ER/PR+ breast cancers.

1.1.2 Study Drug

1.1.2.1 MLN0128

mTOR Inhibitors

The mTOR serine/threonine kinase has a central role in regulating cellular growth and metabolism in response to external environmental factors.[19,20] 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).[21] The TORC2 complex is activated by growth factors and promotes cell survival, proliferation, and actin cytoskeleton organization by phosphorylating and activating kinases, such as AKT kinase (also known as protein kinase B), which is a regulator of apoptosis.[22,23]

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.[20] Thus, rapamycin and the rapalogs are only partial inhibitors of TORC1.[20]

The ATP-competitive inhibitors (also known as mTOR kinase inhibitors or TORKinibs), such as MLN0128 (also known as TAK-228), 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.[24-26]

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 above) or loss of S6K-mediated feedback inhibition of growth factor receptor signaling leading to paradoxic hyperactive signaling. The normal feedback loop involves activated S6K, which phosphorylates and inactivates insulin receptor substrate-1 and inhibits signaling through the PI3K pathway.[23,27] 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.[20,23,27]

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 TORC1 in a dose- and schedule-dependent manner with near complete inhibition of S6K.[28] Half the paired tumor samples had a posttreatment increase in the phosphorylation of AKT at S473.[28] 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.

Clinical Evidence Supporting the Use of mTOR Inhibitors in Breast Cancer

The utility of targeting the PI3K/AKT/mTOR signaling pathway to overcome or ameliorate endocrine therapy resistance has been evaluated in 2 randomized clinical trials in postmenopausal women with metastatic breast cancer. In the phase 3 study Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2), 724 postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer who developed progressive disease while on nonsteroidal AI therapy were randomized in a 2:1 ratio to receive either the steroidal AI exemestane in combination with everolimus or exemestane plus placebo.[29] At the interim analysis, the median progression-free survival (PFS) was longer in patients who received the combination of exemestane and everolimus compared with those who received exemestane and placebo, according to both local assessments by the investigators (6.9 versus 2.8 months) and a central assessment (10.6 versus 4.1 months).[29] In a smaller, open-label, phase 2 study (TAMRAD study), postmenopausal women with hormone receptor-positive, HER2-negative, and AI-resistant metastatic breast cancer were stratified according to primary or secondary hormone resistance and randomized to receive either tamoxifen and everolimus (n=54) or tamoxifen alone (n=57).[30] The 6-month clinical

benefit rate (CBR), defined as the percentage of patients who achieved complete response (CR) or partial response or stable disease (SD) at 6 months, was higher for patients who received the combination of tamoxifen and everolimus compared with those who received tamoxifen alone (61% [95% CI of 47 to 74] versus 42% [95% CI of 29 to 56]).[30] Both of these studies demonstrated that targeting the PI3K/AKT/mTOR signaling pathway with everolimus can overcome acquired resistance to antiestrogen agents in postmenopausal women with hormone receptor-positive, AI-resistant breast cancer.

The results of the clinical trials of everolimus in postmenopausal women with hormone receptor-positive, AI-resistant breast cancer demonstrate the clinical utility of targeting the PI3K/AKT/mTOR signaling pathway with a rapalog to overcome resistance to antiestrogen therapy in this population. However, it is likely that patients receiving everolimus may develop resistance to everolimus due to the loss of feedback inhibition and subsequent TORC2-induced activation of AKT, which is suggested by the pharmacodynamic results from a phase 1 study with everolimus.[28] The goal of this study (C31001) is to test the hypothesis that acquired resistance to combination antihormonal treatment with everolimus in patients with hormone receptor-positive breast cancer is due to feedback reactivation of PI3K/AKT signaling and that antihormonal sensitivity can be restored by targeting this pathway with the dual TORC1/2 inhibitor MLN0128.

1.2 Nonclinical Experience

MLN0128, also known as INK-0128, is an orally available, potent, and highly selective ATP competitive inhibitor of mTOR kinase that exhibits dual specificity against both the TORC1 and TORC2 complexes. MLN0128 is a second-generation mTOR inhibitor that targets the kinase domain of the mTOR enzyme to suppress TORC1 and TORC2 functions, a feature believed to increase the antitumor effect relative to currently available mTOR inhibitors, which as a class, are derivatives of rapamycin and referred to as rapalogs. These agents are TORC1-only inhibitors and operate through a distinct mechanism to MLN0128.

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

CSNK1D, CSNK1E, DDR1, MEK1, MEK2, PDGFRα, and RIPK2). MLN0128 also displays potent cellular inhibition of both the TORC1 and TORC2 pathway with cellular pharmacodynamic concentration producing 50% inhibition 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.[31] 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.[31-33] Dual TORC1/2 inhibition mitigates the feedback activation of AKT, which is known to cause resistance to TORC1-only inhibitors such as rapamycin.[34] 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.

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Additional details related to nonclinical experience with MLN0128 may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

1.3.1 Clinical Experience With MLN0128

Single-agent MLN0128 is in clinical development with 2 phase 1 studies in patients with advanced solid malignancies (INK128-001) and in patients with relapsed or refractory multiple myeloma or Waldenström macroglobulinemia (INK128-002). A third phase 1 study of MLN0128 is in combination with paclitaxel with or without trastuzumab in patients with advanced solid tumors (INK128-003). These studies have been designed to investigate the safety, PK, pharmacodynamics, and preliminary efficacy of MLN0128 for the treatment of

advanced solid tumors and hematologic malignancies either as a single agent or in combination with chemotherapy and/or HER2-targeting agents. Additionally, the combination of MLN0128 with MLN1117 (an oral PI3Kα inhibitor) is being evaluated in a phase 1b study in adult patients with advanced nonhematologic malignancies (Study C32001).

Refer to the current edition of the IB for updated summaries of the clinical experience with MLN0128.

1.3.1.1 Clinical PK of MLN0128

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

The PK properties of MLN0128 are detailed in the IB.

1.4 Study Rationale

The primary objective of this phase 1b/2 study is to evaluate the safety and efficacy of MLN0128, in combination with either exemestane or fulvestrant, in postmenopausal women with estrogen receptor-positive/human epidermal growth factor receptor-2-negative (ER+/HER2–) advanced or metastatic breast cancer with disease progression after previous treatment with everolimus (in combination with either exemestane (any country) or fulvestrant [US only]).

The PI3K/AKT/mTOR pathway is often activated in ER/PR+ breast cancer with approximately 20% to 25% of tumors harboring activating PIK3CA mutations and 15% to 35% having loss of the PTEN tumor suppressor protein.[7,35,36] Beyond this, several lines of evidence suggest that reactivation of the pathway is a cellular response to long-term estrogen deprivation and plays a key role in acquired antiestrogen resistance.[18,37,38] Combined targeting of both ER and PI3K/AKT/mTOR pathways, as demonstrated by the BOLERO-2[29] and TAMRAD[30] studies, is a promising and proven therapeutic approach for ER/PR+ breast cancer.

MLN0128 is a potent, highly selective, ATP-competitive inhibitor of mTOR. MLN0128 is mechanistically distinct from the allosteric inhibitors of mTOR (rapamycin and its derivatives, referred to as rapalogs). The rapalogs only partially inhibit TORC1, whereas MLN0128 inhibits both TORC1 (more completely S6K and 4E-BP1) and TORC2. Dual TORC1/2 inhibition mitigates feedback activation of PI3K and AKT, known to cause resistance to TORC1-only inhibitors, such as everolimus.[34]

MLN0128 administered in combination with antihormonal therapy may restore sensitivity to antihormonal treatments in patients who have progressed on such therapies in combination with everolimus.

Rationale for Starting Dose of MLN0128

The starting doses of 5 mg MLN0128 and 4 mg MLN0128, in combination with exemestane or fulvestrant, are both predicted to provide an area under the plasma concentration versus time curve (AUC) that will be above those considered bioactive in nonclinical pharmacology studies conducted in tumor xenograft models and associated with stasis. The 4 mg once daily (QD) dose of MLN0128 already provides daily plasma exposures that are comparable to those observed with a 10 mg QD dose of the TORC1 inhibitor everolimus, after accounting for differences in plasma protein binding and in-vitro cell proliferation assay inhibitory potency for each agent.

The single-agent maximum tolerated dose (MTD) of MLN0128 for continuous QD dosing established in the escalation phase of Study INK128-001 is 6 mg QD; however, a substantial number of patients required dose modification after prolonged exposure at this dose. The expansion phase of Study INK0128-001 has established that 5 mg QD is the recommended phase 2 dose of MLN0128. Because no PK-based drug-drug interactions (DDIs) between MLN0128 and either exemestane or fulvestrant are expected, it is projected that the plasma exposures of MLN0128 in combination with either exemestane or fulvestrant will be less than those at the respective single-agent exposures at the MLN0128 MTD of 6 mg QD.

Part 1 of the phase 1 portion of the study will initiate with enrollment of 6 patients at the starting dose of 5 mg QD of MLN0128 capsules based on unmilled active pharmaceutical ingredient (API) in combination with either exemestane (at the established dose) or high-dose fulvestrant (500 mg intramuscular [IM] once a month). After completing 2 cycles of treatment with MLN0128 (Cycle 2 Day 28) in combination with either exemestane or fulvestrant, a safety and tolerability assessment will be performed.

Part 2 of the phase 1 portion of the study will initiate with enrollment of 6 patients at a starting dose of 3 mg QD of MLN0128 capsules based on milled API. The starting dose of 3 mg was chosen to account for the possibility of increased absorption with MLN0128 capsules based on milled API and on emerging safety data from Part 1 of the phase 1b portion of this study with MLN0128 dosing at 5 mg QD in combination with either exemestane (any country) or fulvestrant (US only). During Part 2 of the phase 1 portion of this study:

- If ≥2 dose-limiting toxicities (DLTs) occur in the treatment group receiving 4 mg of MLN0128, the subsequent phase 2 portion of the study will be initiated at 3 mg of MLN0128 QD in combination with exemestane or fulvestrant.

- If ≤1 DLT occurs in the treatment group (either at 4 mg or 2 mg QD), the subsequent phase 2 portion of the study will be initiated at the same dose (either 2 mg or 4 mg of MLN0128 QD) in combination with exemestane or fulvestrant.

- If ≥2 DLTs occur in the treatment group receiving 2 mg of MLN0128 in combination with either exemestane and/or fulvestrant, the study will be stopped.

Based on the outcome of a safety and tolerability analysis performed in the phase 1b portion of the study, MLN0128 4 mg QD in combination with either exemestane or fulvestrant was determined as the Phase 2 starting dose. Another safety and tolerability assessment will be performed during the phase 2 portion of the study where the first 6 patients treated with MLN0128 (4 mg QD) in combination with exemestane (any country) or fulvestrant (US only) who have completed 2 cycles of treatment with MLN0128 will be evaluated for treatment-emergent adverse events (TEAEs). Enrollment of patients into the study will continue during this safety and tolerability assessment.

In addition, during the phase 2 portion of the study, both tolerability and need for dose reductions and/or modifications will continue to be monitored for all patients in all cycles. If, based on this assessment, the 4 mg QD starting dose identified in Part 2 of the phase 1 portion is deemed unfavorable, in conjunction with agreement of the study investigators and the medical monitor, the starting dose may be adjusted to 2 or 3 mg QD, respectively, for all newly enrolled patients to improve long-term tolerability. Patients who were enrolled at 3 or 4 mg QD in Part 2 of the phase 1 portion and the phase 2 portion will be maintained at this dose unless dose modifications are required due to individual tolerability. A starting dose

reduction, if required, will be documented to all study sites by formal written communication.

1.4.1 Mutual DDI Assessment

Mutual DDI Assessment Between MLN0128 and Exemestane

Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that MLN0128 is metabolized primarily via cytochrome P450 (CYP) 1A2 (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.

MLN0128 neither inhibited nor induced any of the major CYP enzymes. MLN0128 did not inhibit P-glycoprotein but did inhibit breast cancer resistance protein at a relatively high concentration not expected at the dose of 5 mg QD proposed for administration to patients in this study. In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with MLN0128 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers (see Section 14.4) should be administered only with caution and at the discretion of the investigator during the study.

Exemestane is metabolized by various CYP enzymes, including CYP3A4, CYP1A1>2A6, and 4A11. Exemestane did not inhibit any of the major CYP enzymes (CYP1A2, 2C9, 2D6, 2E1, or 3A4). Exemestane did not affect the PK of tamoxifen, a CYP3A4 substrate, in clinical DDI studies, suggesting a low risk for DDI with other CYP3A4 substrates. Ketoconazole, a potent CYP3A4 inhibitor, did not significantly affect the PK of exemestane, but rifampin, a potent CYP3A4 inducer, decreased exemestane exposure by approximately 41%.[39] Inducers of CYP3A4 (such as rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) should be avoided during this study (refer to Section 6.4).

It is not known if exemestane is a substrate for any of the major drug transporters. Based on the available information for both of these agents, the risk of a clinically meaningful DDI between MLN0128 and exemestane can be considered low.

To assess this risk, steady-state, serial PK samples will be collected to quantify both MLN0128 and exemestane. The PK data collected for this assessment will be compared against historic PK data for the respective agents to evaluate the risk for mutual DDI between these agents.

Mutual DDI Assessment Between MLN0128 and Fulvestrant

A mutual DDI assessment between MLN0128 and fulvestrant is not planned in this study. Fulvestrant is metabolized by numerous biotransformation pathways (including oxidation by CYP3A4) and is not known to inhibit any of the major CYP enzymes. No meaningful change in fulvestrant PK was observed when co-administered with ketoconazole (a potent CYP3A4 inhibitor), rifampin (a potent CYP3A4 inducer), or midazolam (a CYP3A4 substrate).[40] Collectively, this information suggests a low risk for DDI between MLN0128 and fulvestrant.

In addition, fulvestrant is administered IM, and its peak plasma concentrations, when administered by this route, are observed approximately 168 hours (or 7 days) after dosing. Fulvestrant also has a plasma half-life of approximately 40 days, making it difficult to fully characterize the PK of fulvestrant.[40] Based on this information, and given the relatively low risk for DDI between MLN0128 and fulvestrant, no serial PK samples will be collected for mutual DDI assessment between these agents; however, sparse PK samples will be collected to characterize the PK of MLN0128 (as a population PK assessment). Population PK analysis can then be used to assess clinically meaningful changes in the PK of MLN0128, when co-administered with fulvestrant.

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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, and blood creatinine increased.

During the phase 1 portion of the study, risk mitigation strategies for potential adverse events (AEs) include criteria for determining DLTs. Additionally, in both the phase 1 and phase 2 portions of the 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 AEs and serious adverse events (SAEs) by the sponsor.

The potential benefits of MLN0128 are discussed in Section 1.1.2.1.

Further details are presented in the IB.

Refer to the most recent US Prescribing Information (USPI) or the Summary of Product Characteristics (SmPC) for exemestane and fulvestrant for information regarding potential risks and benefits for these medications.[39,40]

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives include:

Phase 1b

- To evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

Phase 2

- To evaluate the antitumor activity by CBR at 16 weeks (CBR-16; defined as the proportion of patients who achieve CR or partial response of any duration or have SD at 16 weeks) of treatment with MLN0128 in combination with either exemestane or fulvestrant.

2.2 Secondary Objectives

The secondary objectives include:

- To further evaluate the antitumor activity of MLN0128 in combination with either exemestane or fulvestrant.
- To evaluate the PK of MLN0128 and exemestane when administered in combination and to evaluate the PK of MLN0128 when administered in combination with fulvestrant.
- To assess the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

2.3 Exploratory Objectives

The exploratory objectives include:

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3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints include:

Phase 1b

- AEs, SAEs, assessments of clinical laboratory values, vital sign measurements, physical examination findings, and electrocardiograms (ECGs).

Phase 2

- CBR-16.

3.2 Secondary Endpoints

The secondary endpoints include:

- CBR at 24 weeks (CBR-24; defined as the proportion of patients who achieve CR or partial response of any duration or have SD at 24 weeks).
- Overall response rate (ORR; defined as best response of CR or partial response).
- PFS.
- Overall survival (OS).
- Change in tumor size from Baseline.
- Steady-state PK parameters of MLN0128 and exemestane including, but not limited to, single-dose maximum (peak) concentration (C_{max}), T_{max}, AUC from zero to 24 hours (AUC_{24h}), AUC from zero to the last measurable concentration (AUC_t), and $t_{1/2}$.
- AE, SAEs, assessments of clinical laboratory values, vital sign measurements, physical examination findings, and ECGs.

3.3 Exploratory Endpoints

The exploratory endpoints include:

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4. STUDY DESIGN

4.1 Overview of Study Design

This is a phase 1b/2 study of the safety and efficacy of MLN0128 in combination with exemestane or fulvestrant therapy in women with ER+/HER2– advanced or metastatic breast cancer that has progressed on treatment with everolimus in combination with exemestane (any country) or fulvestrant (US only). Patients enrolled in this study will be given the same prior therapy (either exemestane or fulvestrant) at their established dose.

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. MLN0128 will be administered in 28-day treatment cycles.

4.1.1 Phase 1b

In the phase 1b portion of the study, the safety and tolerability of MLN0128 using a capsule formulation based on unmilled (Part 1) and milled (Part 2) API in combination with either

exemestane (any country) or fulvestrant (US only) will be evaluated. Patients enrolled in Part 1 will remain on MLN0128 capsules based on unmilled API. Patients will be enrolled as follows:

Part 1 (Capsules Based on Unmilled API):

MLN0128+Exemestane Safety Cohort: Six patients will receive MLN0128 capsule formulation based on unmilled API (5 mg QD) in combination with exemestane (administered per prior therapy for the patient). Steady-state serial PK samples will be collected to quantify both MLN0128 and exemestane to characterize the PK of MLN0128 and exemestane when administered in combination.

MLN0128+Fulvestrant Safety Cohort (US Only): Six patients will receive MLN0128 capsule formulation based on unmilled API (5 mg QD) in combination with high-dose fulvestrant (500 mg IM every month). After completing 2 cycles of treatment with MLN0128 (Cycle 2 Day 28) in combination with fulvestrant, a safety and tolerability assessment will be performed. If ≥2 DLTs occur in either treatment group (exemestane or fulvestrant) after completing 2 cycles of treatment with MLN0128 (5 mg QD), the dose of MLN0128 will be reduced in that treatment group (MLN0128 in combination with exemestane or MLN0128 in combination with fulvestrant) to 4 mg QD for patients subsequently enrolled in the phase 2 portion study (refer to Section 6.2 for additional details).

Part 2 (Capsules Based on Milled API):

MLN0128+Exemestane (Any Country)/Fulvestrant (US Only) Safety Cohort 1: Six patients will receive MLN0128 capsule formulation based on milled API (3 mg QD) in combination with either exemestane or fulvestrant. Serial blood samples will be collected to evaluate the PK of MLN0128 when administered in combination with either exemestane or fulvestrant. After the last patient completes Cycle 1, a safety and tolerability assessment will be performed. If ≥2 DLTs occur in these 6 patients, the dose of MLN0128 will be reduced to 2 mg QD for patients subsequently enrolled in Cohort 2 of Part 2 of the phase 1b portion of this study. If ≤1 DLT occurs in Cohort 1, the dose of MLN0128 will be escalated to 4 mg QD for patients entering Cohort 2.

MLN0128+Exemestane (Any Country)/Fulvestrant (US Only) Safety Cohort 2: Six patients will receive MLN0128 capsule formulation based on milled API, either

4 or 2 mg QD based on the safety observed in Cohort 1, in combination with either exemestane or fulvestrant. Serial PK samples will be collected as outlined for Cohort 1. After the last patient completes Cycle 1, a safety and tolerability assessment will be performed.

- If ≥2 DLTs occur in the treatment group receiving 4 mg of MLN0128, the subsequent phase 2 portion of the study will be initiated at 3 mg of MLN0128 QD in combination with exemestane or fulvestrant.

- If ≤1 DLT occurs in the treatment group (either at 4 or 2 mg QD), the subsequent phase 2 portion of the study will be initiated at the same dose (either 2 or 4 mg of MLN0128 QD) in combination with exemestane or fulvestrant.

- If ≥2 DLTs occur in the treatment group receiving 2 mg of MLN0128 in combination with either exemestane and/or fulvestrant, the study will be stopped.

Enrollment in the phase 2 portion of the study will commence for patients on MLN0128 in combination with exemestane or fulvestrant therapy once the safety assessment has been completed for the phase 1b portion of the study. Patients enrolled in phase 1b will not be eligible for participation in phase 2.

Based on the outcome of a safety and tolerability analysis performed in the phase 1b portion of the study, MLN0128 4 mg QD in combination with either exemestane or fulvestrant was determined as the phase 2 starting dose. Another safety and tolerability assessment will be performed during the phase 2 portion of the study where the first 6 patients treated with MLN0128 4 mg QD in combination with exemestane or fulvestrant who have completed 2 cycles of treatment with MLN0128 will be evaluated for TEAEs. Enrollment of patients into the study will continue during this safety and tolerability assessment.

In addition, during the phase 2 portion of the study, both tolerability and need for dose reductions and/or modifications will continue to be monitored for all patients in all cycles. If, based on this assessment, the 4 mg QD starting dose identified in Part 2 of the phase 1 portion is deemed unfavorable, in conjunction with agreement of the study investigators and the medical monitor, the starting dose may be adjusted to 2 mg or 3 mg QD, respectively, for all newly enrolled patients to improve long-term tolerability. Patients who were enrolled at 3 mg or 4 mg QD in Part 2 of the phase 1 portion and the phase 2 portion will be maintained at this dose unless dose modifications are required due to individual tolerability.

A starting dose reduction, if required, will be documented to all study sites by formal written communication.

4.1.2 Phase 2

In the phase 2 portion of the study, the safety and efficacy of MLN0128 in combination with either exemestane (any country) or fulvestrant (US only) will be evaluated. Patients will be administered MLN0128 at 4 mg QD in combination with either exemestane (any country) or fulvestrant (US only), based on the outcome of the safety and tolerability analysis performed in the phase 1b portion of the study.

Patients will be enrolled into one of 2 parallel cohorts, depending on the quality and/or duration of their prior response to everolimus in combination with either exemestane (any country) or fulvestrant (US only) as follows:

> **Everolimus-Resistant Cohort:** This is a cohort of 56 response-evaluable patients who have progressed on treatment with everolimus in combination with either exemestane (any country) or fulvestrant (US only) without achieving an objective response (CR or partial response) or after achieving SD for <6 months as their best response. Patients will receive MLN0128 in combination with the same dose of the previously administered treatment (exemestane [any country] or fulvestrant [US only]).
>
> **Everolimus-Sensitive Cohort**: This is a cohort of 48 response-evaluable patients who have progressed on treatment after achieving a CR or partial response of any duration, or SD ≥6 months with prior everolimus treatment in combination with either exemestane (any country) or fulvestrant (US only). Patients will receive MLN0128 in combination with the same dose of the previously administered treatment (exemestane [any country] or fulvestrant [US only]).

Sparse PK samples will be collected from all patients enrolled in the study (regardless of whether they are administered MLN0128 in combination with exemestane or fulvestrant) for plasma PK analysis of MLN0128 only. Blood samples for all PK analyses will be collected at the time points specified in the Phase 1b Pharmacokinetic and ECG Sample Breakdown and the Phase 2 Pharmacokinetic and ECG 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.

Radiographic tumor evaluations will be performed on contrast-enhanced imaging (CT scan with intravenous [IV] contrast or magnetic resonance imaging [MRI] with IV contrast), unless contraindicated. CT of the chest, and CT or MRI of the abdomen and pelvis, will be used to evaluate disease response according to RECIST version 1.1.[42] Supplemental x-ray and/or bone scanning may be performed, but these methods are not suitable for lesion measurement. Radiographic tumor evaluations will be performed by the investigator at the time points specified in the Schedule of Events.

Throughout the study, 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.[43] Definitions of DLTs for the phase 1 portion of the study are in Section 6.2 and dose modification guidelines for the phase 2 portion of the study are in Section 6.3.

AEs will be assessed, and clinical laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

4.2 Number of Patients

Approximately 128 patients will be enrolled in this study from approximately 40 study centers in the US, Belgium, and France. A patient will be considered enrolled after receiving the first dose of MLN0128.

4.3 Duration of Study

Patients will receive MLN0128 in combination with either exemestane (any country) or fulvestrant (US only) until they experience disease progression. Patients will discontinue treatment with MLN0128 if they have an unacceptable drug-related toxicity. The maximum duration of treatment will be 24 months. If after discussion between the investigator and sponsor it is determined that a patient would derive benefit, the patient may continue treatment beyond 24 months. The study will be terminated 6 months after the last patient completes an End-of-Treatment (EOT) study visit.

Patients will attend an EOT/Early Termination visit 30 to 40 days after receiving their last dose of MLN0128 or at the start of subsequent anticancer therapy. After EOT, patients will be followed for PFS and OS. For those patients who discontinue MLN0128 for any reason other than radiographic disease progression, contrast-enhanced imaging (CT or MRI scans)

should be completed to further assess disease progression (per RECIST, version 1.1).[42] See Section 7.10 for additional posttreatment follow-up details.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

5.1.1 Phase 1b and Phase 2

1. Advanced or metastatic breast cancer.

2. Histological or cytological confirmation of ER+ status (defined as >1% positive tumor cells), and histological or cytological confirmation of HER2-negative (HER2-) status by local laboratory testing using criteria in the American Society of Oncology (ASCO)/College of American Pathologists (CAP) Clinical Practice Guideline update.[44]

3. Female patients 18 years of age or older who:

   - Are postmenopausal for at least 1 year before the Screening visit, where menopause is defined by:
     - Age ≥55 years and 1 year or more of amenorrhea.
     - Age <55 years and 1 year or more of amenorrhea, with an estradiol assay <20 pg/mL.
     - Surgical menopause with bilateral oophorectomy.

   Note: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.

4. Patients who have a history of brain metastasis are eligible for the study provided that **all** the following criteria are met:

   - Brain metastases which have been treated.

- No evidence of disease progression for ≥3 months or hemorrhage after treatment.
- Off-treatment with dexamethasone for 4 weeks before administration of the first dose of MLN0128.
- No ongoing requirement for dexamethasone or antiepileptic drugs.

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

6. Clinical laboratory values as specified below within 4 weeks before the first dose of MLN0128:
   - Bone marrow reserve consistent with absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L; platelet count $\geq 100\times10^9$/L; hemoglobin ≥9 g/dL.
   - Total bilirubin ≤1.5 times the upper limit of the normal range (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN (≤ 5×ULN if liver metastases are present).
   - Creatinine clearance ≥50 mL/min 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.

7. Left ventricular ejection fraction (LVEF) within 5 absolute percentage points of institutional standard of normal as measured by echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan within 4 weeks before the first dose of MLN0128 (ie, if the institutional standard of normal is 50%, LVEF may be as low as 45% to be eligible for the study).

8. Able to provide paraffin blocks or a minimum of 10 unstained slides of available archival tumor tissues (paraffin blocks are preferred). If archival tumor tissue is not available, a tumor biopsy may be performed before the patient begins treatment with MLN0128. If fewer than 10 slides are available or the tumor content/area requirements are not met, study eligibility will be determined upon discussion with the sponsor.

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

10. Voluntary written consent must be given before the 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.

5.1.2 Phase 1b Only

In addition to the previously mentioned inclusion criteria, each patient must meet the following inclusion criterion to be enrolled in the phase 1b portion of the study:

11. Patients may have SD or disease progression during their most recent treatment with exemestane or fulvestrant, or everolimus in combination with either exemestane (any country) or fulvestrant (US only). Exemestane or fulvestrant in combination with MLN0128 can also be initiated as a new line of therapy.

5.1.3 Phase 2 Only

In addition to the previously mentioned inclusion criteria, each patient must meet all of the following inclusion criteria to be enrolled in the phase 2 portion of the study:

12. Measureable disease defined as follows:

    - At least 1 extraosseous lesion that can be accurately measured in at least 1 dimension. The lesion must measure ≥20 mm with conventional imaging techniques or ≥10 mm with spiral CT or MRI, or

    - Bone lesions (lytic or mixed [lytic plus sclerotic]) in the absence of measurable disease as defined above.

13. Patients must have had disease progression during treatment with everolimus in combination with either exemestane (any country) or fulvestrant (US only) (duration of treatment ≥4 weeks) and must have tolerated everolimus treatment in combination with exemestane (any country) or fulvestrant (US only) adequately according to the treating physician's judgment. Everolimus in combination with exemestane or fulvestrant is not required to be the most recent treatment before enrollment, but progression on the most recent anticancer therapy is required for enrollment.

5.2 Exclusion Criteria

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

5.2.1 Phase 1b and Phase 2

1. Prior anticancer therapy or other investigational therapy within 2 weeks before administration of the first dose of MLN0128 (except for exemestane or fulvestrant, which should be continued). Treatment with everolimus must be discontinued 2 weeks before administration of the first dose of MLN0128.

2. Chronic concomitant therapy with bisphosphonates or denosumab for the prevention of bone metastases. Concomitant treatment with bisphosphonates or denosumab is permitted for treatment of osteoporosis or management of existing bone metastases if initiated at least 4 weeks before administration of the first dose of MLN0128.

3. Exclusion criterion 3 was removed as of Protocol Amendment 6.

4. 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 MLN0128 (patients already receiving erythropoietin on a chronic basis for ≥4 weeks are eligible).

5. Previous treatment with dual PI3K/mTOR inhibitors or TORC1/2 inhibitors.

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

7. Poorly controlled diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >7%; patients with a history of transient glucose intolerance due to corticosteroid administration may be enrolled in this study if all other inclusion/exclusion criteria are met.

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

9. Known human immunodeficiency virus infection.

10. History of any of the following within the last 6 months before administration of the first dose of MLN0128:

    - 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 14.2).
    - Pulmonary embolism.

11. Significant active cardiovascular or pulmonary disease before administration of the first dose of MLN0128, including:

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

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

12. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of MLN0128 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.

5.2.2 Phase 1b Only

In addition to the previously mentioned exclusion criteria, patients meeting the following exclusion criterion are not to be enrolled in the phase 1b portion of the study:

13. More than 3 prior chemotherapy regimens for locally advanced or metastatic disease.

5.2.3 Phase 2 Only

In addition to the previously mentioned exclusion criteria, patients meeting the following exclusion criterion are not to be enrolled in the phase 2 portion of the study:

14. More than 1 prior chemotherapy regimen for locally advanced or metastatic disease.

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of MLN0128 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 all patients, MLN0128 will be administered QD at approximately the same time each day. It is recommended that each dose of MLN0128 be given orally with 8 ounces (240 mL) of water.

- *For patients receiving MLN0128 capsules with unmilled API*: MLN0128 will be administered with a light meal.

- *For patients receiving MLN0128 capsules with milled API*: MLN0128 will be administered on an empty stomach. The 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.

If severe emesis or mucositis prevents the patient from taking an MLN0128 dose, that dose will be skipped. If emesis occurs after study medication ingestion and whole capsule(s) are visible in the vomitus, replacement capsule(s) should be taken; otherwise the dose will not be readministered, 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.

Exemestane and fulvestrant will be administered per their current USPIs or SmPCs, and according to the dose regimen administered before study entry.

For patients assigned to receive MLN0128 in combination with exemestane:

- MLN0128 should be administered first on an empty stomach (ie, nothing to eat or drink for 2 hours before and 1 hour after MLN0128 dosing).

- Patients should have a meal before taking their exemestane dose, which may be taken between 1 and 6 hours after MLN0128 dosing.

6.2 Definitions of DLT for the Phase 1b Portion of the Study

DLTs are defined according to the AE profile observed during the first 28 days of study drug administration in phase 1b of the study and as described below. All AEs should be considered possibly related to the study drug unless such relationship can be definitively excluded. In Part 2 of the phase 1b portion of the study:

- If ≥2 DLTs occur in the treatment group receiving 4 mg of MLN0128, the subsequent phase 2 portion of the study will be initiated at 3 mg of MLN0128 QD in combination with exemestane or fulvestrant.

- If ≤1 DLT occurs in the treatment group (either at 4 mg or 2 mg QD), the subsequent phase 2 portion of the study will be initiated at the same dose (either 2 mg or 4 mg of MLN0128 QD) in combination with exemestane or fulvestrant.

- If ≥2 DLTs occur in the treatment group receiving 2 mg of MLN0128 in combination with either exemestane and/or fulvestrant, the study will be stopped.

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010.[43] These criteria are provided in the Study Manual. A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to treatment with MLN0128 in combination with either exemestane or fulvestrant:

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

Patients who experience an AE that meets the definition of a DLT during or after completing Cycle 1 should have their study drug treatment interrupted. If the event resolves to Grade 1 or baseline values within 2 weeks of interrupting planned therapy, and in the opinion of the investigator and the sponsor's project clinician the benefits of continuing treatment outweigh the risks posed by the toxicity, patients may continue study treatment with MLN0128 at a 25% to 50% dose reduction (ie, dose reduced from 4 mg to 3 mg [25%]; from 3 mg to 2 mg [33%]; or from 2 mg to 1 mg [50%] QD) with approval of the sponsor's project clinician. Alternatively, if dose modification is required for patients receiving 2 mg QD, then the dosing frequency may also be decreased to 5 days per week (28% reduction) instead of

decreasing the daily dose administered. If study drug dosing is delayed for more than 14 consecutive days for MLN0128-related toxicity, despite supportive treatment per standard clinical practice, or more than 2 dose reductions of MLN0128 are required, the patient will be discontinued from the study.

6.3 Dose-Modification Guidelines for the Phase 2 Portion of the Study

6.3.1 Dose Modification or Treatment Delay for MLN0128-Related Toxicity

Based on the outcome of a safety and tolerability analysis performed in the phase 1b portion of the study, MLN0128 4 mg QD in combination with either exemestane or fulvestrant was determined as the phase 2 starting dose. Another safety and tolerability assessment will be performed during the phase 2 portion of the study where the first 6 patients treated with MLN0128 4 mg QD in combination with exemestane or fulvestrant who have completed 2 cycles of treatment with MLN0128 will be evaluated for TEAEs. Enrollment of patients into the study will continue during this safety and tolerability assessment.

In addition, during the phase 2 portion of the study, both tolerability and need for dose reductions and/or modifications will continue to be monitored for all patients in all cycles. If, based on this assessment, the 4 mg QD starting dose identified in Part 2 of the phase 1 portion is deemed unfavorable, in conjunction with agreement of the study investigators and the medical monitor, the starting dose may be adjusted to 2 or 3 mg QD for all newly enrolled patients to improve long-term tolerability. Patients who were enrolled at 3 or 4 mg QD in Part 2 of the phase 1 portion and the phase 2 portion will be maintained at this dose unless dose modifications are required due to individual tolerability. A starting dose reduction, if required, will be documented to all study sites by formal written communication.

MLN0128 administration should be withheld for MLN0128-related toxicities that are ≥Grade 3 despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 or baseline values within 2 weeks of interrupting treatment, the patient may resume study treatment at a 25% to 50% dose reduction (ie, 2 mg QD). Alternatively, if dose modification is required for patients receiving 2 mg QD, then the dosing frequency should be decreased to 5 days per week instead of decreasing the daily dose administered. If MLN0128 dosing is delayed for more than 14 consecutive days for MLN0128-related toxicity despite supportive treatment per standard clinical practice, or more than 2 dose reductions of MLN0128 are required in a patient, stop MLN0128 therapy, discontinue the patient from the study, and complete the EOT visit within 30 to 40 days after the last dose of

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

6.4 Excluded Concomitant Medications and Procedures

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient as of the first MLN0128 administration through 30 days following the last dose will be recorded on the designated case report form.

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).
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of an MLN0128-related AE (eg, rash).
- Strong CYP1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator (see Section 14.4 for a list of these agents).
- Antiepileptic drugs for patients with a history of treated brain metastasis.
- Concomitant administration of any proton pump inhibitor (PPI) is not permitted during the study. Patients receiving PPI therapy before enrollment must stop using the PPI for 7 days before their first dose of study drugs. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
- Histamine H2 receptor antagonists may be allowed, if needed provided that the histamine H2 receptor antagonist is not taken within 12 hours before and within 6 hours after study drug administration. Patients receiving histamine H2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H2 receptor antagonists include ranitidine, famotidine, and nizatidine. Cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist (see Section 14.4).

- Administration of neutralizing antacids and calcium preparations is permitted except from 4 hours before until 2 hours after MLN0128 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.

6.5 Permitted Concomitant Medications and Procedures

Prophylactic use of antiemetic (including ondansetron and granisetron), antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose of MLN0128, as needed throughout the study before each dosing, and as clinically indicated per standard practice.

Concomitant treatment with bisphosphonates is permitted for treatment of osteoporosis or management of existing bone metastases if initiated at least 4 weeks before administration of the first dose of MLN0128. Bisphosphonates should be given after Cycle 1 to minimize confounding factors that may contribute to potential drug-related toxicities.

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

6.6 Precautions and Restrictions

No dietary restrictions will be imposed on study patients other than daily fasting for glucose monitoring (refer to Section 7.4.16).

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

6.7 Management of Clinical Events

6.7.1 Management of Hyperglycemia

In addition to obtaining fasting serum glucose levels at the clinic visits as outlined in the Schedule of Events, all patients will be provided with a glucometer and trained in its use to monitor their daily predose fasting blood glucose (FBG) levels at home. 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 6 consecutive months, then the frequency of in-home fasting glucose testing may be reduced to twice weekly if the investigator approves. Patients will continue to notify the investigator of FBG levels ≥150 mg/dL, and if blood glucose levels are not well controlled, or if they require either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. Guidelines for management of hyperglycemia are presented in Table 6-1.

Table 6-1 Management of Hyperglycemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	FBG>ULN–160 mg/dL	Continue close monitoring of blood glucose. Initiate oral hypoglycemic agent.	None
2	FBG>160–250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥ 3	FBG>250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤Grade 2. Resume MLN0128 based on timing of recovery: • ≤1 week: resume at same dose and schedule. • >1 but ≤2 weeks: reduce dose. (a) • 2 weeks: stop MLN0128 and discontinue patient from the study.
Prevention/Prophylaxis • Follow fasting serum glucose levels during clinic visits. • Monitor home glucometer test results. • Check HbA1c levels every 3 months during therapy. • Recommend lifestyle modifications, as appropriate (balanced diet, limited alcohol consumption, increased physical activity). • Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy is recommended to prevent higher-grade hyperglycemia. • FBG levels ≥150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.			

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

(a) Phase 1b Part 1 cohorts: for patients receiving a starting dose of 5 mg, reduce by 20% (to 4 mg). If dose modification is required for patients receiving ≤4 mg QD, then the frequency of dosing should be decreased to QD×5D, rather than decreasing the daily dose administered. For all other patients: the initial dose reduction should be from 4 mg to 3 mg, with further reduction to 2 mg if necessary.

If any fasting serum glucose reading performed at the site indicates hyperglycemia (>ULN or ≥110 mg/dL), the study staff should first confirm that the patient was fasting at the time

of the blood draw (ie, nothing by mouth for at least 8 hours before). To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines are provided to aid the investigator in initiating antiglycemic therapies.

Based on the clinical experience in MLN0128 trials, most episodes of hyperglycemia observed have been Grade 1 or Grade 2 and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since instituting a standard regimen for early treatment of hyperglycemia. All patients developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting serum glucose>ULN≤160 mg/dL) or consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with ≥Grade 2 hyperglycemia (fasting serum glucose >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 of 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.

6.7.2 Management of Hyperlipidemia

Guidance on MLN0128 dose modification for patients with hyperlipidemia is provided in Table 6-2.

Table 6-2 Management of Hyperlipidemia

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

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

(a) Phase 1b Part 1 cohorts: for patients receiving a starting dose of 5 mg, reduce by 20% (to 4 mg). If dose modification is required for patients receiving ≤4 mg QD, then the frequency of dosing should be decreased to QD×5D, rather than decreasing the daily dose administered. For all other patients: the initial dose reduction should be from 4 mg to 3 mg, with further reduction to 2 mg if necessary.

6.7.3 Management of Oral Mucositis

Guidance for the management of oral mucositis is provided in Table 6-3.

Table 6-3 Management of Oral Mucositis

Grade	Description	Treatment	MLN0128 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 MLN0128 dosing until recovery to ≤Grade 1. Reinitiate at same dose.
3	Severe pain interfering with oral intake	Same as for Grade 2; consider intralesional corticosteroids.	Hold dose until recovery to ≤Grade 1, then restart with a dose reduction. (a)
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.

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

(a) Phase 1b Part 1 cohorts: for patients receiving a starting dose of 5 mg, reduce by 20% (to 4 mg). If dose modification is required for patients receiving ≤4 mg QD, then the frequency of dosing should be decreased to QD×5D, rather than decreasing the daily dose administered. For all other patients: the initial dose reduction should be from 4 mg to 3 mg, with further reduction to 2 mg if necessary.

6.7.4 Management of Rash

Guidance for management of rash is provided in Table 6-4.

Table 6-4 Management of Rash

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

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

(a) Phase 1b Part 1 cohorts: for patients receiving a starting dose of 5 mg, reduce by 20% (to 4 mg). If dose modification is required for patients receiving ≤4 mg QD, then the frequency of dosing should be decreased to QD×5D, rather than decreasing the daily dose administered. For all other patients: the initial dose reduction should be from 4 mg to 3 mg, with further reduction to 2 mg if necessary.

6.7.5 Management of Nausea and/or Vomiting

Guidance for the management of nausea and/or vomiting is provided in Table 6-5.

Table 6-5 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 MLN0128 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.

6.7.6 Management of Noninfectious Pneumonitis

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

Table 6-6 Management of Noninfectious Pneumonitis

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

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

(a) Phase 1b Part 1 cohorts: for patients receiving a starting dose of 5 mg, reduce by 20% (to 4 mg). If dose modification is required for patients receiving ≤4 mg QD, then the frequency of dosing should be decreased to QD×5D, rather than decreasing the daily dose administered. For all other patients: the initial dose reduction should be from 4 mg to 3 mg, with further reduction to 2 mg if necessary.

6.8 Blinding and Unblinding

This is an open-label study.

6.9 Description of Investigational Agents

MLN0128 will be supplied as capsules for oral administration. MLN0128 is available in 3 dose strengths, 1 mg, 3 mg, and 5 mg, each containing 1 mg, 3 mg, and 5 mg of MLN0128, respectively, in addition to the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant), and hard gelatin capsule.

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

- 1 mg MLN0128 capsules: white opaque color.

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

The original MLN0128 capsules based on unmilled API will continue to be supplied to support treatment for ongoing patients in Part 1 of the phase 1b portion of the study. The new MLN0128 capsules based on milled API will be administered to patients in Part 2 of the phase 1b and the phase 2 portions of the study.

Exemestane is a commercially available oral drug supplied as tablets.[39] Fulvestrant is a commercially available drug administered as an IM injection.[40]

6.10 Preparation, Reconstitution, and Dispensation

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

MLN0128 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 capsules.

6.11 Packaging and Labeling

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

Supplies of the new MLN0128 capsules based on milled API will be accompanied with a new label to differentiate them from the existing supplies of the MLN0128 capsules that are based on unmilled API.

While the patient is enrolled in the study, exemestane and fulvestrant may be supplied either by the site from commercial sources (US sites) or provided by Millennium (ex-US sites). When provided by Millennium, exemestane and fulvestrant will be appropriately labeled in compliance with local and regional regulations.

6.12 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN0128 should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F to 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 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 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will receive instructions for home storage and administration of MLN0128. Patients will also receive diary cards to record dosing compliance of MLN0128, the appropriate combination therapy (exemestane or fulvestrant), and instructions for their completion.

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

Please refer to the Study Manual for additional instructions.

Exemestane and fulvestrant should be stored according to instructions provided in the manufacturer's most recent package insert or SmPC.

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 Millennium Study Monitor 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

For Part 1 of the phase 1b portion of the study, all enrolled patients will be assigned to receive MLN0128 capsules based on unmilled API at 5 mg QD in combination with either fulvestrant or exemestane, at the same dose previously administered.

For Part 2 of the phase 1b portion of the study, the first 6 patients (Cohort 1) will be assigned to receive MLN0128 capsules based on milled API at 3 mg QD with either exemestane or fulvestrant, at the same dose previously administered. Based on safety and tolerability assessments of Cohort 1, an additional 6 patients (Cohort 2) will then be assigned to receive MLN0128, at either 4 or 2 mg QD, in combination with either exemestane or fulvestrant.

Enrollment in the phase 2 portion of the study will commence for patients on MLN0128 in combination with exemestane or fulvestrant therapy once the safety assessment has been completed for the phase 1b portion of the study.

Additional details regarding treatment cohorts are provided in Section 4.1.

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, and ethnicity 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 the disease. In addition, concomitant medications will be recorded as specified in Section 7.4.10.

For patients enrolling into phase 2 (only) who have measurable disease and are undergoing CT scans (rather than MRIs) for tumor assessment, the most recent CT scan performed before their baseline CT scan in this study will be collected, if available, and forwarded to a third-party vendor for tumor volume/size analysis (see Section 8.1.7.3). The date of the scan should be indicated, if known. Availability of the scan is not a prerequisite for study eligibility.

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 ECOG Performance Status

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

7.4.8 MUGA Scan or ECHO

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

7.4.9 Pregnancy Test

Pregnancy testing will not be performed in this study as enrollment is restricted to postmenopausal women only.

7.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from first dose of MLN0128 through 30 days after the last dose. See Section 6.4 and Section 6.5 for a list of medications and therapies that are prohibited and/or permitted during the study.

7.4.11 AEs

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.

7.4.12 Enrollment

A patient is considered to be enrolled in the study when the first dose of MLN0128 is administered. Procedures for completing the enrollment information are described in the Study Manual.

7.4.13 ECG

A single, 12-lead ECG will be administered at the time points specified in the Schedule of Events and in the Phase 1b Pharmacokinetic and ECG Sample Breakdown and the Phase 2 Pharmacokinetic and ECG Sample Breakdown table. Additional ECGs may be obtained as clinically indicated.

7.4.14 Clinical Laboratory Evaluations

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

Clinical Chemistry, Hematology/Coagulation, 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 MLN0128.

Hematology/Coagulation

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 and coagulation panels include the following:

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (ANC)
- Activated partial thromboplastin time (aPTT)
- Prothrombin time/international normalized ratio (PT/INR)

Clinical Chemistry

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

The clinical chemistry panel includes the following:

- Blood urea nitrogen
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase
- Gamma glutamyl transferase
- Phosphate
- Albumin
- Alkaline phosphatase
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide
- Magnesium
- Amylase
- HbA1c (only at the time points specified in the Schedule of Events)

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

Fasting Lipid Profile

Prospective monitoring for hyperlipidemia will be managed through fasting lipid testing at the time points specified in the Schedule of Events.

The fasting lipid profile includes the following:

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

7.4.15 Fasting Serum Glucose

Fasting serum glucose will be measured at the time points specified in the Schedule of Events before administration of MLN0128. 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.

7.4.16 In-Home Daily Fasting Glucose Monitoring

Patients will be instructed to complete daily glucose monitoring at home after fasting overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) for each of these measurements. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded into source documents. Based on investigator judgment, and upon the 6 consecutive months of well-controlled blood glucose levels, the frequency of in-home fasting glucose testing may be reduced to twice weekly. During this period of reduced monitoring, patients will continue to notify the investigator of FBG levels that exceed 150 mg/dL. If blood glucose levels are not well controlled at any time during the study, or if the patient requires either oral

hypoglycemic agents or insulin to control blood glucose levels, in-home testing of FBG levels will be resumed daily with the provided glucometer. On study visit days where fasting glucose is assessed in the clinic, the in-home daily fasting glucose monitoring does not need to be completed.

7.4.17 Disease Assessment

Patients will undergo contrast-enhanced imaging (CT or MRI) to monitor the overall disease burden unless contraindicated for a particular patient in accordance with RECIST 1.1 [25], where measureable disease is defined as at least 1 extraosseous lesion that can be accurately measured in at least 1 dimension.[42] Anatomical measurements (summed across target lesions) will be collected at Baseline and at each subsequent evaluation using an imaging modality consistent with that used at Screening. As much as possible, the same imaging modalities and methods should be used for patients throughout the study. CT scans of the chest, in addition to CTs or MRIs of the abdomen and pelvis, will be obtained at Screening and all subsequent time points. Supplemental x-ray and/or bone scanning may be performed, but these methods are not suitable for lesion measurement. Objective assessments will be performed at each time point specified in the Schedule of Events. When possible, the same qualified physician will interpret results to reduce variability.

In the absence of measurable disease at Baseline, the following will be considered disease progression among patients with bone-only disease:

- The appearance of 1 or more new lytic lesions in bone.
- The appearance any extraosseous lesions.
- Unequivocal progression of existing bone lesions.

Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents. The sponsor may request electronic images for those patients who demonstrate a response. Digital Imaging and Communications in Medicine-formatted images of radiologic scans will be electronically transferred to a third-party vendor for a centralized assessment of tumor volumes/sizes.

7.4.18 PK Measurements

PK samples collected in this study will be used to quantify MLN0128 or exemestane only. The plasma concentration of fulvestrant will not be measured in this study. The dates and

exact times when MLN0128 and exemestane were administered and the dates and exact times at which PK samples were obtained will be noted in the eCRF. Blood samples will be collected at the time points specified in the Phase 1b Pharmacokinetic and ECG Sample Breakdown and the Phase 2 Pharmacokinetic and ECG Sample Breakdown tables.

7.4.19 Archival (Banked) Tumor Tissue and Tumor Biopsies

CCI [redacted]

7.4.20 DNA Measurements

Blood samples will be collected at the time points specified in the Schedule of Events, and CCI [redacted]

CCI [redacted]

Such analysis will be exploratory in nature and may or may not be completed as part of this study assessment; hence, the deliverable of the results from such analyses will not adhere to this study's timelines. CCI [redacted] The results of such analyses will thus not be presented in the clinical study report for this study and will be presented in a separate population PK analysis report at a later time.

7.4.21 CCI

CCI

7.5 Completion of Treatment

Patients will be considered to have completed treatment if they discontinue MLN0128 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 and Patient Replacement

Treatment with MLN0128 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.

Once MLN0128 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 MLN0128 discontinuation will be recorded on the eCRF.

Patients in the Everolimus-Resistant Cohort and in the Everolimus-Sensitive Cohort who are not response evaluable (refer to Section 8.1.3) will need to be replaced.

Note that some patients may discontinue MLN0128 for reasons other than progressive disease. These patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events and in Section 7.10.

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 patient.
- 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 MLN0128 for each treatment cycle and a diary in which to record their dosing. Patients should continue taking the same dose of either exemestane or fulvestrant as previously administered. The study center staff will check the patient's diary versus the patient's supply of remaining MLN0128 and either exemestane or fulvestrant 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.

7.10 Posttreatment Follow-up Assessments (PFS and OS)

After EOT, patients will be followed for PFS and OS. 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. For those patients who discontinue MLN0128 for any

reason other than radiographic disease progression, CT (with contrast) or MRI scans (with contrast, unless contra-indicated) should be completed to further assess disease progression (per RECIST, version 1.1).[42] Refer to the Schedule of Events for appropriate assessments during posttreatment follow-up.

The study (including the posttreatment follow-up period) will be terminated 6 months after the last patient completes an EOT study visit.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to MLN0128 that occur during the posttreatment follow-up. Refer to Section 9 for details regarding definitions, documentation, and reporting of SAEs.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

8.1.1 Determination of Sample Size

Phase 1b

The safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant will be evaluated. Patients will be enrolled as follows:

- In Part 1 of the phase 1b portion of the study, up to 6 patients will be enrolled into the MLN0128+Exemestane Safety Cohort and up to 6 patients will be enrolled into the MLN0128+Fulvestrant Safety Cohort. The number of patients is based on clinical considerations.

- In Part 2 of the phase 1b portion of the study, 6 patients will be enrolled into MLN0128+Exemestane/Fulvestrant Safety Cohort 1, and 6 patients will be enrolled into MLN0128+Exemestane/Fulvestrant Safety Cohort 2. The number of patients is based on clinical considerations.

Phase 2

The sample size for each cohort in the phase 2 portion of the study is based on a standard Simon two-stage design. A Bayesian predictive probability design was used to allow multiple interim analyses to stop early for futility.[45] See Section 8.1.9 for sample size

assumptions. Up to 56 response-evaluable patients will be enrolled in the Everolimus-Resistant Cohort. In the Everolimus-Sensitive Cohort, up to 48 response-evaluable patients will be enrolled.

8.1.2 Randomization and Stratification

This study will not require randomization or stratification.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: patients who receive at least 1 dose of MLN0128.
- PK population: patients with sufficient dosing and PK data to reliably estimate PK parameters.
- Response-Evaluable population: patients who receive at least 1 dose of MLN0128 and have measurable disease at Baseline.

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.

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 (age, race, weight, height, and other parameters as appropriate) will be summarized by drug combination (MLN0128 in combination with exemestane and MLN0128 in combination with fulvestrant) in the phase 1b portion of the study and by cohort (Everolimus-Sensitive Cohort and Everolimus-Resistant Cohort) in the phase 2 portion of the study.

8.1.6 Efficacy Analysis

Analysis of efficacy measures will be descriptive. Investigators will assess disease response according to RECIST guidelines (version 1.1)[42] at each time point. The best overall

response for each patient will be derived programmatically from among the reported responses at the end of Cycle 4 and for the entire treatment period.

Data listings will present the tumor measurements on contrast-enhanced CT or MRI (including changes from Baseline) scans, disease response category (eg, CR, partial response, and SD), and other endpoints as appropriate.

Primary Efficacy Endpoint

The primary efficacy endpoint in the phase 2 portion of the study is CBR-16.

The number and percentage of patients achieving clinical benefit at 16 weeks will be tabulated, and the estimate of the CBR-16 will be presented with a 2-sided 95% exact binomial CI for each cohort.

Secondary Efficacy Endpoints

The number and percentage of patients in each response category (CR, partial response, SD, disease progression, ORR, CBR-24, and CBR) will be tabulated for each cohort.

PFS is defined as the time from the date of first MLN0128 administration to the date of first documentation of disease progression or death. OS is defined as the time from the date of first MLN0128 administration to the date of death. PFS and OS will be analyzed using Kaplan-Meier methodology for each cohort.

Waterfall plots of the best percentage of change from Baseline in the sum of the longest diameter (SLD) of the target lesion will be generated for each cohort.

8.1.7 PK/Pharmacodynamics/Biomarkers

8.1.7.1 PK Analysis and Modeling

Individual patient plasma concentration–time data and individual patient concentration–time plots for MLN0128 and exemestane will be provided as listings. Additionally, mean concentration–time data for MLN0128 and exemestane will be provided.

Data permitting, PK parameters including, but not limited to, C_{max}, T_{max}, AUC_{24h}, AUC_t, and $t_{1/2}$ will be reported for MLN0128 and exemestane.

A formal DDI assessment between MLN0128 and exemestane is not planned in this study; however, for the purpose of assessment of DDI between MLN0128 and exemestane, plasma

concentration–time data and relevant PK parameters (such as C_{max}, AUC_{24h}, and $t_{1/2}$) of MLN0128 and exemestane will be compared against historical, single-agent PK data for these agents. The PK of MLN0128 and exemestane on Cycle 1 Day 15 will be assessed based on evaluable patients from the MLN0128+Exemestane Safety Cohort. Blood samples for PK analysis may be required from patients from other cohorts where MLN0128 is administered in combination with exemestane to obtain an appropriate sample size for the DDI assessment.

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. The results of population PK analysis will be presented in a separate report.

8.1.7.2 CCI

CCI

8.1.7.3 CCI

CCI

CCI

[redacted]

8.1.8 Safety Analyses

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 MLN0128 and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of MLN0128 and through 30 days after the last dose of MLN0128 will be tabulated.

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

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

A listing of TEAEs resulting in MLN0128 discontinuation will be provided.

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

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from Baseline to the worst postbaseline value.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term by cohort in the safety population.

Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile.

ECG Analysis

ECG intervals (QT and QTc with Fridericia correction, PR, and QRS) and ventricular rate will be summarized at each scheduled time point, along with mean change from Baseline to each posttreatment time point. The number and percentage of patients with ECG abnormalities will be summarized at each time point.

8.1.9 Interim Analysis

There will be 3 interim analyses for futility in the Everolimus-Resistant Cohort and 2 interim analyses for futility in the Everolimus-Sensitive Cohort. The investigator-assessed CBR-16 rate will be used as the endpoint for the interim analysis. The interim analysis will be based on response-evaluable patients who have had the opportunity to complete a minimum of 4 cycles of treatment with MLN0128 or have discontinued treatment with MLN0128 before the end of Cycle 4.

In the Everolimus-Resistant Cohort, there will be 3 interim analyses based on the following assumptions:

- Ineffective CBR-16 rate (H_o): 10%.
- Effective CBR-16 rate (H_a): 20%.
- Alpha=10%; power=80%.
- Prior Beta Distribution Parameters: ao=0.10, b0=0.90.
- Probability of early termination under H_o: 68%.

Table 8-1 Interim Analyses in the Everolimus-Resistant Cohort

Stage	No. of Patients Evaluated	Number of Patients With CBR-16 to Proceed or Declare Active
1	29	≥ 3
2	39	≥ 4
3	49	≥ 6
Final	56	≥ 9

In the Everolimus-Sensitive Cohort, there will be 2 interim analyses based on the following assumptions:

- Ineffective CBR-16 rate (H_o): 15%.
- Effective CBR-16 rate (H_a): 30%.
- Alpha=5%; power=80%.
- Prior Beta Distribution Parameters: ao=0.15, b0=0.85.
- Probability of early termination under H_o: 71%.

Table 8-2 Interim Analyses in the Everolimus-Sensitive Cohort

Stage	No. of Patients Evaluated	Number of Patients With CBR-16 to Proceed or Declare Active
1	23	≥4
2	38	≥7
Final	48	≥12

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 MLN0128.

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 Definition

Serious AE 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.[43] Clarification should be made between a serious AE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

9.2 Procedures for Recording and Reporting 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 MLN0128 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 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.[43] 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 MLN0128 through 30 days after administration of the last dose of MLN0128 and recorded in the eCRFs.

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of MLN0128 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 MLN0128 through 30 days after administration of the last dose of MLN0128 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

Reporting drug exposure during pregnancy and birth events is not applicable for this study as enrollment is restricted to postmenopausal women only.

9.5 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 (EMA), 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. 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 MLN0128 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 eCRF Completion

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

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

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

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

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

10.4 Study Monitoring

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

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

10.5 Ethical Considerations

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

10.6 Patient Information and Informed Consent

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

10.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, MLN0128 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 MLN0128 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 MLN0128 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/ [redacted] and report the complaint. **The contact information is as follows**:

Medical Information Call Center:	CCI [redacted]
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 CCI [redacted] (refer to Section 9.2).

10.12 Closure of the Study

The study (including the posttreatment follow-up period) will be terminated 6 months after the last patient completes an EOT study visit.

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.

10.13 Record Retention

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

11. USE OF INFORMATION

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

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

12. INVESTIGATOR AGREEMENT

I have read Protocol C31001 Amendment 6: A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2– Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant.

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

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

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

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14. APPENDICES

14.1 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, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[48]

14.2 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.[49]

14.3 Cockcroft-Gault Equation

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

OR

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[50]

14.4 List of Relevant CYP Inhibitors and Inducers

Moderate CYP1A2 Inhibitors		
Cimetidine	Methoxsalen	
Strong CYP1A2 Inhibitors		
Fluvoxamine	Ciprofloxacin	
Clinically Significant Enzyme Inducers		
Carbamazepine	Rifabutin	St. John's wort
Phenobarbital	Rifampin	Phenytoin
Rifapentine		

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

14.5 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

The primary purpose of this amendment is to expand the number of investigative sites to include sites in the United States (US), Belgium, and France. In conjunction with this expansion, it has been noted that Millennium will provide exemestane and fulvestrant to sites outside of the US and references to the Summary of Product Characteristics (SmPCs) for each agent have been added. This amendment also incorporates procedural clarifications that were contained in prior administrative letters and clarifies posttreatment follow-up procedures, including a specification for an overall study ending time point.

To optimize analysis of the phase 2 exploratory endpoint of [redacted]

Several eligibility criteria have been clarified. The inclusion criterion for human epidermal growth factor receptor 2 (HER2)-negative status was simplified to reference the updated HER2 testing criteria of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP). The exclusion criterion for treatment with cytochrome P450 (CYP) inhibitors has been aligned with the prohibited concomitant medications.

The revisions and clarifications in this protocol amendment are listed below.

Purposes for Amendment 1

The purposes of this amendment are to:

Study Administration

- Increase the number of investigative sites to approximately 40, including sites in the US, Belgium, and France
- Add the EudraCT (European Clinical Trials Database) number
- Update the contact information for the reporting of serious adverse events in both the US and the rest of the world (incorporates Administrative Letter #1, 06 December 2013)
- Specify that the study will end no later than 6 months after the last patient completes the end-of-treatment visit

Eligibility

- Refine the HER2-status inclusion criterion by clarifying the language and revising the reference histologic criteria to conform with the recently updated ASCO/CAP recommendations for HER2 testing in breast cancer
- Align the eligibility criteria with the list of prohibited concomitant medications regarding moderate inhibitors of CYP2C9
- Clarify that patients enrolled in the phase 1b portion are not eligible to participate in the phase 2 portion of the study

Study Drug and Investigational Agents

- Replace "study drug" with "MLN0128" where applicable, for clarity
- Specify that MLN0128 should be taken once daily at approximately the same time each day
- Specify that exemestane and fulvestrant will be provided by Millennium Pharmaceuticals, Inc., to the investigative sites located outside of the US
- Clarify that patients in the phase 1b portion who receive exemestane as their prior therapy will continue their therapy at their previously established dose
- Reference the current version of the SmPC for exemestane and fulvestrant in addition to the US Prescribing Information

Procedures and Assessments

- Clarify that information on concomitant medications is collected from the time of the first dose of MLN0128 through 30 days after last dose of MLN0128 (incorporates Administrative Letter #2, 06 February 2014)
- Clarify the language regarding food and beverage restrictions
- Simplify the wording of the definition of dose-limiting toxicity in phase 1b
- Revise the procedure subsection heading to emphasize that either (but not both) a multiple gated acquisition scan or echocardiogram should be performed (incorporates Administrative Letter #2, 06 February 2014)
- Specify that coagulation assessments are required for all patients at the time points listed in the Schedule of Events
- Specify that the coagulation assessments are included in the list of hematology assessments in the clinical laboratory evaluations section
- Clarify that glycosylated hemoglobin testing is required only at the time points specified in the Schedule of Events (incorporates Administrative Letter #2, 06 February 2014)
- Clarify that tumor responses are based on RECIST (Response Evaluation Criteria in Solid Tumors) guidelines (Version 1.1), without any modification
- Add a request for the most recent historical prebaseline CT scans (if available) for patients enrolling into phase 2 who have measurable disease
- CCI [redacted]
- CCI [redacted]
- Clarify the procedures for posttreatment follow-up
- Add 2 assumptions to the interim analyses for futility

Administrative

- Delete a description of the overall safety profile of MLN0128 because the IB is intended to be the primary source of safety information pertaining to the drug candidate

- Update the List of Abbreviations and Glossary of Terms to include ASCO, CAP, and SmPC
- Insert a cross-reference in Section 8.1.1 to Section 8.1.9 to direct the reader to the sample size assumptions for this study
- Correct typographical errors, punctuation, grammar, and formatting

14.6 Amendment 2 Rationale and Purposes

Rationale for Amendment 2

Clinical Study Protocol C31001 is being amended to evaluate the safety, tolerability, and pharmacokinetics (PK) of a new MLN0128 capsule based on milled active pharmaceutical ingredient (API) before initiation of the phase 2 portion of the study. The new capsules based on milled API are to be taken on an empty stomach.

Purposes for Amendment 2

The purposes of this amendment are to:

The purposes of this amendment are to:

- Evaluate the safety, tolerability, and PK of a new MLN0128 capsule based on milled API (Part 2 of the phase 1b portion of the study)
- Add 12 patients to be enrolled into the study
- Add blood sampling for PK analysis in Part 2 of the phase 1b portion of the study
- Provide rationale for the starting dose of the new MLN0128 capsules based on milled API
- Update dose-limiting toxicity (DLT) definitions for patients in Part 2 of the phase 1b portion of the study
- Update information on dose reductions in patients in the phase 1b portion of the study
- Update information on dose reductions in patients in the phase 2 portion of the study
- Provide clarification on drug supply information for the MLN0128 capsules based on unmilled and milled API
- Provide information on packaging and labeling of the new MLN0128 capsules based on milled API
- Provide information on treatment group assignment for patients in Part 2 of the phase 1b portion of the study
- Provide instruction that MLN0128 capsules with milled API will be taken on an empty stomach, but capsules with unmilled API will continue to be taken with a light meal
- Remove PK sampling in the phase 2 part of the study on Cycle 2, Day 15 and Cycle 3, Day 8 for all patients and replace with PK samples on Cycle 1, Day 15 and Cycle 2, Day 1
- Clarify the PK and ECG sampling time points for the 2 phases of the study

- Provide clarification in the description of statistical analyses used to determine sample size in the phase 2 portion of the study
- Correct the assumptions for the interim analysis of the Everolimus-Sensitive Cohort in the phase 2 portion of the study
- Provide clarification in the inclusion criteria that exemestane or fulvestrant in combination with MLN0128 can also be initiated as a new line of therapy in patients enrolled into the phase 1b portion of the study
- Provide clarification that concomitant treatment with denosumab is permitted for treatment of osteoporosis or management of existing bone metastases
- Correct typographical errors, punctuation, grammar, and formatting

14.7 Amendment 3 Rationale and Purposes

Rationale for Amendment 3

Clinical Study Protocol C31001 is being amended to clarify that enrolled patients in France or Belgium will not have had prior combination therapy with fulvestrant and everolimus, and will not receive this combination in the study. Additionally, this amendment clarifies the timing of MLN0128 and exemestane administration to allow for exemestane to be administered after a meal in accordance with the product label. Lastly, a guide for managing patients with noninfectious pneumonitis has been added, and the vendor and contact information to report product complaints has been updated.

Purposes for Amendment 3

The purposes of this amendment are to:

- Clarify in the inclusion criteria that patients with advanced or metastatic breast cancer in the United States (US) would have received prior everolimus in combination with either exemestane or fulvestrant, whereas patients outside of the US participating in this trial would have received prior everolimus in combination with exemestane, but not fulvestrant.
- Clarify that, because of the change in the inclusion criteria, patients enrolled in any country may receive MLN0128 plus exemestane, but only patients enrolled in the US may receive MLN0128 plus fulvestrant.
- Clarify that patients in the MLN0128 + fulvestrant safety cohort will be in the US and will receive the combination of MLN0128 + fulvestrant, not MLN0128 + exemestane.
- Clarify that MLN0128 should be administered first on an empty stomach, and exemestane administered after a meal, between 1 and 6 hours after MLN0128 dosing, with the following exception: For patients in the phase 2 PK/Tumor-PD Cohort, during Cycle 1 only, MLN0128 and exemestane should be administered at the same time, on an empty stomach.

- Clarify in the Schedule of Events that a confirmatory scan is to be performed approximately 4 weeks after a previous scan for all patients with a complete or partial response.
- Provide guidance for the management of patients with noninfectious pneumonitis.
- Update the vendor and contact information for reporting product complaints.
- Correct typographical errors, punctuation, grammar, and formatting.

14.8 Amendment 4 Rationale and Purposes

Rationale for Amendment 4

This amendment modifies the eligibility criteria to expand the pool of potential study participants and to clarify disease status confirmation requirements, and decreases the number of PK samples required in the phase 2 portion of the study. This amendment also revises the excluded medications section of the protocol based on characterization of PK from the phase 1 portion of this study and other clinical studies in the MLN0128 development program. The starting dose for the phase 2 portion of this study has also been confirmed as 4 mg (milled) MLN0128 + either exemestane 25 mg or fulvestrant 500 mg, based on a safety and tolerability review of patients in Cohort 2 of phase 1b Part 2. It is not anticipated that these modifications will affect the scientific integrity of the study or the safety of study participants.

Administrative changes have been made such as introducing the new compound code for the study drug, adding the suspected unexpected serious adverse reactions (SUSAR) language, and revising the product complaints vendor and contact information. Additional minor clarifications or corrections have been made as necessary.

Purposes for Amendment 4

The purposes of this amendment are to:

- Expand eligibility criteria to:
    - Allow enrollment of patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 at baseline (previously baseline ECOG status must have been 0 to 1; see inclusion criterion #5).
    - Remove the requirement that everolimus in combination with exemestane or fulvestrant must be the most recent anticancer therapy prior to enrollment (see inclusion criterion #13).
    - Allow prior treatment with PI3K inhibitors, AKT inhibitors, or TORC1 inhibitors (see exclusion criterion #5).
- Clarify the requirements for confirmation of ER+/HER2- status, separate from the requirement of metastatic or advanced breast cancer (see inclusion criteria #1 and #2).
- Decrease the number of PK samples required of patients in the phase 2 portion:
    - For patients in the PK/Tumor PD cohort on Cycle 1 Day 15 replace 6 serial PK samples (predose, and 0.5, 1, 2, 4, and 8 hours postdose) with a single

sample to be collected at the time of the Cycle 1 Day 15 biopsy (2-4 hours after the MLN0128 dose).
    - For all other patients in phase 2 on Cycle 1 Day 15, a single PK sample will be collected at 2-hours postdose.
    - For all patients in phase 2 on Cycle 2 Day 1, replace 3 serial PK samples (0.5, 2, and 4 hours postdose) with 2 samples that can be collected any time during the Cycle 2 Day 15 clinic visit, with the second sample to be collected 1 hour after the first.
- For patients in the phase 2 PK/Tumor PD Cohort:
    - Remove PK assessment of exemestane.
    - Remove requirement for taking exemestane at the same time as MLN0128 and on an empty stomach during Cycle 1.
- Add clinical laboratory testing for fasting lipid profile on Cycle 2 Day 1.
- Modify excluded medications based on characterization of PK from the phase 1 portion of this study and other clinical studies, and revise text describing the excluded medications to align with the other phase 2 protocols in the MLN0128 development program:
    - Do not exclude the concomitant use of a drug needed by patients that has a potential to be a moderate CYP2C9 inhibitor, pending follow-up with the study investigator and the medical monitor.
    - Exclude concomitant PPI therapy on study.
    - Provide guidelines for use of histamine H2 receptor antagonists, neutralizing antacids, and calcium preparations.
    - Replace the list of Relevant Cytochrome P450 Inhibitors and Inducers with the most current information and revise the source citation.
- Confirm that the starting dose of MLN0128 for all phase 2 patients is 4 mg, based on a safety and tolerability review of patients in Cohort 2 of phase 1b Part 2.
- Add clarification regarding dose modifications depending on starting dose:
    - The previous recommendation to change from daily dosing to dosing on 5 consecutive days per week for patients receiving doses ≤4 mg was applicable only to patients in the phase 1b Part 1 portion of the study.
    - The previous recommendation to reduce the dose by 20% also applies only to patients in the phase 1b Part 1 portion of the study; new dose reduction recommendations (from 4 mg to 3 mg, and then to 2 mg if needed) have been added for patients in the phase 2 portion.
- Provide more explicit guidance to the investigator when prescribing any concomitant strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9.
- Introduce the new compound code “TAK-228” for MLN0128.
- Add the suspected unexpected serious adverse reactions (SUSARs) reporting section, clarifying the sponsor’s responsibilities for reporting expected and unexpected adverse events (AEs).

- Change the product complaint reporting vendor and contact information.
- Modify text for consistency across sections.
- Correct typographical errors, punctuation, grammar, and formatting.

14.9 Amendment 5 Rationale and Purposes

Rationale for Amendment 5

This amendment updates the instructions for antiemetic therapy, updates the definition of the Response-Evaluable population, and removes the Pharmacokinetic/Tumor-Pharmacodynamic Cohort.

Purposes for Amendment 5

The purposes of this amendment are to:

- Allow the use of ondansetron and granisetron for antiemetic therapy and prophylaxis.
    - This change was made to relax the constraints on antiemetic therapy and prophylaxis permitted in the study.
- Update the definition of the Response-Evaluable population.
    - This change was made to allow patients without a postbaseline scan to count as evaluable.
- Remove the Pharmacokinetic/Tumor-Pharmacodynamic Cohort.
    - This change was made because data from the planned analyses for this cohort were not needed to support development of the study drug.

14.10 Amendment 6 Detailed Summary of Changes

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

The primary change occurs in Section 5.2 Exclusion Criteria:

Amended or new wording:	3. ~~Treatment with strong inhibitors and/or inducers of CYP3A4, CYP2C19, and CYP2C9 must be discontinued at least 1 week before administration of the first dose of MLN0128.~~ **Exclusion criterion 3 was removed as of Protocol Amendment 6.**

Rationale for Change:
This change, which removes enrollment restrictions for patients taking CYP3A4, CYP2C9, or CYP2C19 inhibitors and/or inducers in this study, was made on the basis of updated data on MLN0128 metabolism by specific CYP isoforms.

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

The primary change occurs in Section 6.4 Excluded Concomitant Medications and Procedures:

Initial wording:	• Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9 should be administered with caution and at the discretion of the investigator only if no other reasonable alternatives without such CYP inhibitory properties are available within the pharmacotherapeutic class and considered suitable for the patient. (Refer to Section 14.4 for a list of strong inhibitors and strong inducers of CYP2C9, CYP2C19, and CYP3A4.) …. • [….]Examples of histamine H2 receptor antagonists include ranitidine, famotidine, nizatidine, and cimetidine.
Amended or new wording:	• Strong ~~CYP3A4 and CYP2C19~~**CYP1A2** ~~inducers and/or~~ inhibitors and ~~moderate inhibitors of CYP2C9~~ **CYP** inducers should be **avoided during Cycle 1 and** administered with caution and at the discretion of the investigator ~~only if no other reasonable alternatives without such CYP inhibitory properties are available within the pharmacotherapeutic class and considered suitable for the patient.~~ (~~Refer to~~ **See Section 14.4 for a list of these agents**~~.~~**).** … • … Examples of histamine H2 receptor antagonists include ranitidine, famotidine**, and** nizatidine.~~,~~ ~~and~~ ~~c~~**Cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist (see Section 14.4).**

Rationale for Change:
This change was made to update the recommendations on concomitant medication use during the study on the basis of updated data on MLN0128 metabolism by specific CYP isoforms.

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

The primary change occurs in Section 14.4 List of Relevant CYP Inhibitors and Inducers:

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

Rationale for Change:

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

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

The primary change occurs in Section 6.4 Excluded Concomitant Medications and Procedures:

Deleted text	~~In addition to the above medications, consumption of grapefruit or grapefruit juice is not permitted during the study. Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study (See Section 14.4).~~

Rationale for Change:
This change was made for consistency with new data that removes the necessity for restrictions concerning CYP2C9 and 2C19.

The following sections also contain this change:

- Section 6.6 Precautions and Restrictions.
- Section 14.4 List of Relevant CYP Inhibitors and Inducers.

Change 5: Clarify language surrounding the use of contrast with MRI.

The primary change occurs in Section 7.4.17 Disease Assessment:

Initial wording:	Patients will undergo CT (with contrast) as appropriate to monitor and assess disease progression, using RECIST guidelines (version 1.1), where measureable disease is defined as at least 1 extraosseous lesion that can be accurately measured in at least 1 dimension.[42] Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Anatomical measurements (summed across target lesions) will be collected at Baseline and at each subsequent evaluation using an imaging modality consistent with that used at Screening. Objective assessments will be performed at each time point specified in the Schedule of Events. When possible, the same qualified physician will interpret results to reduce variability.

Amended or new wording:	Patients will undergo **contrast-enhanced imaging (**CT ~~(with contrast~~ **or MRI**~~)~~ ~~as appropriate~~ to monitor ~~and assess~~ the **overall disease** ~~progression,~~ **burden unless contraindicated for a particular patient** ~~using~~ **in accordance with** RECIST ~~guidelines (version~~ 1.1~~)~~ [25], where measureable disease is defined as at least 1 extraosseous lesion that can be accurately measured in at least 1 dimension.[42] ~~Specific disease sites that cannot be adequately imaged by CT may be documented by MRI.~~ Anatomical measurements (summed across target lesions) will be collected at Baseline and at each subsequent evaluation using an imaging modality consistent with that used at Screening. **As much as possible, the same imaging modalities and methods should be used for patients throughout the study. CT scans of the chest, in addition to CTs or MRIs of the abdomen and pelvis, will be obtained at Screening and all subsequent time points. Supplemental x-ray and/or bone scanning may be performed, but these methods are not suitable for lesion measurement.** Objective assessments will be performed at each time point specified in the Schedule of Events. When possible, the same qualified physician will interpret results to reduce variability.

Rationale for Change:
This language was changed to clarify that if an MRI is used for imaging, contrast is preferred unless contraindicated.

The following sections also contain this change:

- Schedule of Events footnotes f and g.
- Section 4.1.2 Phase 2.
- Section 4.3 Duration of Study.
- Section 7.10 Posttreatment Follow-up Assessments (PFS and OS).
- Section 8.1.6 Efficacy Analysis.

Change 6: Update the description of potential drug-drug interactions between MLN0128 and exemestane..

The primary change occurs in Section 1.4.1 Mutual DDI Assessment:

Initial wording:	In-vitro, MLN0128 is metabolized by various cytochrome P450 (CYP) enzymes, including 2C19 (35%), 3A4 (28%), and 2C9 (28%); MLN0128 neither inhibited nor induced any of the major CYP enzymes. Additionally, MLN0128 did not inhibit P-glycoprotein but did inhibit breast cancer resistance protein at a relatively high concentration not expected at the dose of 5 mg QD proposed for administration to patients in this study.
Amended or new wording:	**Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that MLN0128 is metabolized primarily via cytochrome P450 (CYP) 1A2 (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.

~~In vitro, MLN0128 is metabolized by various cytochrome P450 (CYP) enzymes, including 2C19 (35%), 3A4 (28%), and 2C9 (28%);~~ MLN0128 neither inhibited nor induced any of the major CYP enzymes. ~~Additionally~~, MLN0128 did not inhibit P-glycoprotein but did inhibit breast cancer resistance protein at a relatively high concentration not expected at the dose of 5 mg QD proposed for administration to patients in this study. **In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with MLN0128 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers (see Section 14.4) should be administered only with caution and at the discretion of the investigator during the study.**

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

Change 7: Update the signature page.

The primary change occurs on the signature page of the amendment.

Deleted text	PPD
Amended or new wording	PPD

Rationale for Change:
This change was made to reflect changes in staffing for this project.

Amendment 6 – A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2? Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	01-Nov-2017 13:06 UTC
	Biostatistics Approval	01-Nov-2017 14:24 UTC
	Clinical VP Approval	10-Nov-2017 19:40 UTC