Certain information within this clinical study report has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

CLINICAL STUDY PROTOCOL MLN1117-1501 AMENDMENT 3

MLN1117

A Phase 1b/Adaptive Phase 2 Study of Docetaxel With or Without MLN1117 in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer

Protocol Number:	MLN1117-1501
Indication:	Non-small cell lung cancer
Phase:	1b/2
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2014-004281-25
Therapeutic Area:	Oncology

Protocol History

Original	15 December 2014
Amendment 1	27 April 2015
Amendment 2	29 June 2015
Amendment 3	20 October 2015

Millennium Pharmaceuticals, Inc.
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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.

[redacted] (or designee)	Signature	*Date DD Month YYYY*
[redacted] (or designee)	Signature	*Date DD Month YYYY*
[redacted], Clinical Pharmacology (or designee)	Signature	*Date DD Month YYYY*

Confidentiality Statement
The information contained herein is confidential and the proprietary property of Millennium Pharmaceuticals and any unauthorized use or disclosure of such information without the prior written authorization of Millennium Pharmaceuticals is expressly prohibited.

Rationale for Amendment 3

This amendment is being instituted to expand the Phase 2 eligibility criteria to allow for specific prior therapies, in response to the recent regulatory approval of immune checkpoint inhibitors in the relevant setting.

The amendment also allows for the exploration of alternative dosing regimens of study drug if needed based on emerging study data and consensus between the sponsor and the investigators. Additionally, clarifications to the following are needed: definitions for analysis populations (intent-to-treat [ITT] and response evaluable); stratification factors to be utilized in the randomization scheme for Phase 2 portion of the study; selected statistical methods that will be used for efficacy analyses; and instructions for the centralized storage of copies of Phase 2 radiographic images taken for disease assessment. A restriction for female patients regarding the donation of eggs has been incorporated for consistency with male restrictions. Administrative updates include correction of the estimated number of participating clinical study sites, incorporation of a development code alias for MLN1117 (TAK-117), and updates to the list of sponsor signatories.

Purposes for Amendment 3

The purposes are to:

- Allow for administration of alternative dosing regimens for MLN1117 and for docetaxel under certain circumstances.
- Expand Phase 2 eligibility criteria to allow enrollment of patients who received prior therapy with nivolumab, pembrolizumab, or other immune-checkpoint inhibitors under specific circumstances.
- Define stratification factors to be applied during randomization of Phase 2 enrollment.
- Clarify that during Phase 2 of the study, a copy of all radiographic images taken for the purpose of disease assessment must be sent to the central imaging vendor, and confirm that disease-response evaluations conducted during the study will be based solely on investigator assessment.
- Clarify the ITT population definition.
- Clarify the definition of the Response-Evaluable population and specify the efficacy analyses for which the population will be utilized.
- Clarify the statistical methods to be used in the analyses of primary efficacy endpoints.
- Incorporate a censoring rule for the analysis of overall survival (OS).
- Incorporate a restriction for female patients regarding the donation of eggs.
- Incorporate the development code TAK-117 as a synonym for MLN1117.
- Update the list of sponsor signatories and the estimated number of participating clinical study sites.
- Correct typographical errors, punctuation, grammar, and formatting.

For specific examples and locations of these changes, see Section 14.8.

PROTOCOL SUMMARY

Study Title: A Phase 1b/Adaptive Phase 2 Study of Docetaxel With or Without MLN1117 in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer

Number of Patients: Approximately 75 to 155 total; approximately 15 patients will be enrolled in Phase 1b (dose escalation), and 60 to 140 patients may be enrolled in Phase 2 (dose expansion) based on a sequential, adaptive design.

Study Objectives

Primary

Phase 1b (Dose Escalation)

- To determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of MLN1117 when administered orally in combination with docetaxel in patients with non-small cell lung cancer (NSCLC)

Phase 2 (Dose Expansion)

- To evaluate progression-free survival (PFS) as the primary efficacy measure of MLN1117 plus docetaxel versus docetaxel alone in patients with advanced NSCLC

Secondary

- To evaluate the safety and tolerability of MLN1117 plus docetaxel administered to patients with NSCLC **(Phase 1b and Phase 2)**
- To evaluate the pharmacokinetics (PK) of MLN1117 when administered with docetaxel **(Phase 1b and Phase 2)**
- To evaluate additional efficacy measures, such as response rate, disease control rate, response duration, time to progression, and overall survival (OS), of MLN1117 plus docetaxel versus docetaxel alone in patients with NSCLC **(Phase 2 only)**
- To evaluate PFS and additional efficacy measures of MLN1117 plus docetaxel versus docetaxel alone in different populations of patients with NSCLC, such as patients with squamous NSCLC versus nonsquamous NSCLC, and patients with squamous NSCLC with or without *PIK3CA* mutation and/or amplification (MUT/AMP) **(Phase 2 only)**

Exploratory

- [redacted]
- [redacted]
- [redacted]

Overview of Study Design: This is an open-label, phase 1b/adaptive phase 2 study of MLN1117 in combination with docetaxel versus docetaxel alone in adult patients with NSCLC. This study consists of a Phase 1b dose escalation phase, and an adaptive, randomized Phase 2 expansion phase.

In Phase 1b of the study, the DLTs, MTD, and RP2D of MLN1117 plus docetaxel will be determined using a 3 + 3 dose escalation scheme with a fixed dose of docetaxel and varying dose levels of MLN1117. During a 21-day cycle of treatment, docetaxel (36 mg/m^2) will be administered intravenously (IV) on Days 1 and 8, and MLN1117 tablets (planned doses 300, 600, and 900 mg) will be administered orally on a weekly schedule that includes 3 consecutive dosing days per week (eg, on Days 2, 3, 4, 9, 10, 11, 16, 17, and 18). If MTD or RP2D is not achieved by 900 mg, higher dose levels at 300 mg increments may be evaluated. More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators if such measures are needed for patient safety or for a better understanding of the dose–related toxicity or exposure of MLN1117 plus docetaxel. Additionally during Phase 1b, if MLN1117 de-escalation is warranted, the daily MLN1117 dose may be reduced, or the number of treatment days per week may be reduced (eg, from 3 days to 2 days, or further to 1◦day) while maintaining the same weekly MLN1117 dose. Subsequent escalation may be permitted based on observed safety and tolerability data. These decisions will be made jointly by investigators and the Millennium project clinician. The alternative MLN1117 regimen may be carried forward into Phase 2 of the study if deemed appropriate by the sponsor, in consultation with the investigators.

Testing of escalating MLN1117 doses in combination with a fixed docetaxel dose and schedule is planned. However, if frequent docetaxel dose modifications are necessary when administered in combination with MLN1117, the fixed dose of docetaxel may be decreased (eg, –1 dose level) based on discussion and agreement between investigators and the Millennium project clinician. If decreased, the lower docetaxel dose may be carried forward into Phase 2 of the study if deemed appropriate by the sponsor, in consultation with the investigators.

Patients will be enrolled in the adaptive, randomized Phase 2 portion of the study to evaluate the efficacy of MLN1117 plus docetaxel versus docetaxel alone. The safety and tolerability of MLN1117 administered in combination with docetaxel at the RP2D determined during Phase 1b will also be further characterized. Phase 2 of the study will use a sequential, multistage Bayesian adaptive design and will consist of up to 3 parts evaluating the following patients:

- Part 1: NSCLC (inclusive of both squamous and nonsquamous histology and all *PIK3CA* genotypes)
- Part 2: Histology-specific NSCLC (either squamous or nonsquamous)
- Part 3: Histology- and genotype-specific NSCLC (*PIK3CA* MUT/AMP positive squamous NSCLC if squamous histology is selected in Part 2)

Each part of the adaptive Phase 2 study is designed as a stand-alone, randomized study evaluating PFS as the primary efficacy measure in a distinct population of NSCLC between the 2 treatment arms: MLN1117 plus docetaxel versus docetaxel alone. There will be a primary, event-driven analysis of PFS after each part of Phase 2. Phase 2 will start with Part 1 in NSCLC patients inclusive of all histological types and all *PIK3CA* genotypes (*PIK3CA* mutation, amplification, or wild-type). On the basis of the primary PFS analysis of Part 1, the study may be stopped for efficacy or futility. If neither the efficacy nor the futility boundary is met, a subgroup analysis of PFS based on histology will be performed. The study will proceed to Part 2 if a differential level of efficacy is observed between squamous and nonsquamous and a preferred histology (squamous or nonsquamous) is determined. The primary PFS analysis of Part 2 will in turn determine whether the study should proceed to Part 3, which will evaluate patients with a specific histology and genotype, namely, squamous NSCLC patients with

PIK3CA MUT/AMP if squamous histology is selected for Part 2. Patients will be randomized 1:1 to one of the following treatment arms in Parts 1, 2, and 3 of Phase 2 of the study:

- Arm A: docetaxel 36 mg/m^2 IV on Days 1 and 8 of a 21-day cycle plus MLN1117 tablets, at the dose determined in Phase 1b, on Days 2, 3, 4, 9, 10, 11, 16, 17, and 18 of a 21-day cycle. (An alternative combination dosing regimen may be used based on the RP2D decision in Phase 1b.)
- Arm B: docetaxel 75 mg/m^2 IV once every 3 weeks (per approved prescribing information) with dosing on Day 1 of each 21-day cycle

The treatment duration for all patients in Phase 1b and Phase 2 may be up to 9 cycles of either docetaxel alone or docetaxel in combination with MLN1117. Patients receiving docetaxel plus MLN1117 may continue treatment with MLN1117 monotherapy beyond 9 cycles. Patients may continue to receive treatment until either disease progression, occurrence of unacceptable toxicities, or death. The maximum duration of treatment will be 9 cycles (approximately 6 months) for patients receiving docetaxel alone or12 months for patients receiving MLN117 plus docetaxel (ie, 9 cycles of MLN1117 plus docetaxel followed by MLN1117 alone) unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued treatment beyond 9 cycles or12 months, respectively. Patients may discontinue study treatment at any time. Patients will attend the End-of-Treatment visit 30 to 40 days after receiving their last dose of study drug.

Patients will continue to be followed after discontinuation of study treatment to collect OS data for a period of up to 12 months (after last dose of study treatment). In addition, for patients who discontinue treatment due to reasons other than disease progression, PFS data will be collected during the posttreatment follow-up period of up to 6 months after the last dose of study drug, and OS data collection will continue until death, withdrawal of consent for further follow-up, or 12 months following the last dose of study drug.

Throughout the study, adverse events will be assessed and laboratory values, vital signs, and electrocardiograms will be obtained to evaluate the safety and tolerability of MLN1117 alone or in combination with docetaxel. Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03, effective date 14 June 2010.

Radiological tumor evaluations (computed tomography [CT] scan with IV contrast or magnetic resonance imaging [MRI] as clinically indicated of the chest, abdomen, and pelvis) will be used to evaluate disease response according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1. Radiographic tumor evaluations and disease assessment will be performed by the investigator throughout the study. During the Phase 2 portion of the study, copies of all radiographic images with measurements will be sent to a central imaging vendor for the purpose of retrospective review by the sponsor. However, central radiologic evaluation is not planned for response assessment during the study.

[redacted]

Blood samples for analysis of circulating tumor DNA will be collected at baseline from all patients. Subsequent samples will be obtained during the study and analyzed for the presence and clone frequency of somatic mutations frequently reported in solid tumors including *PIK3CA* mutations. Correlative studies will be performed to compare the mutation data generated from circulating tumor DNA versus tumor tissue DNA. Dynamic changes in mutant clone frequency measured in circulating tumor DNA over the course of treatment will be evaluated in relation to objective response and disease

status.

In addition, archived or fresh biopsy tumor tissue samples collected during screening will be analyzed for somatic alterations and other biomarkers that may relate to sensitivity or resistance to MLN1117 plus docetaxel.

Pharmacokinetic samples will be collected to characterize the PK of MLN1117 when administered in combination with docetaxel.

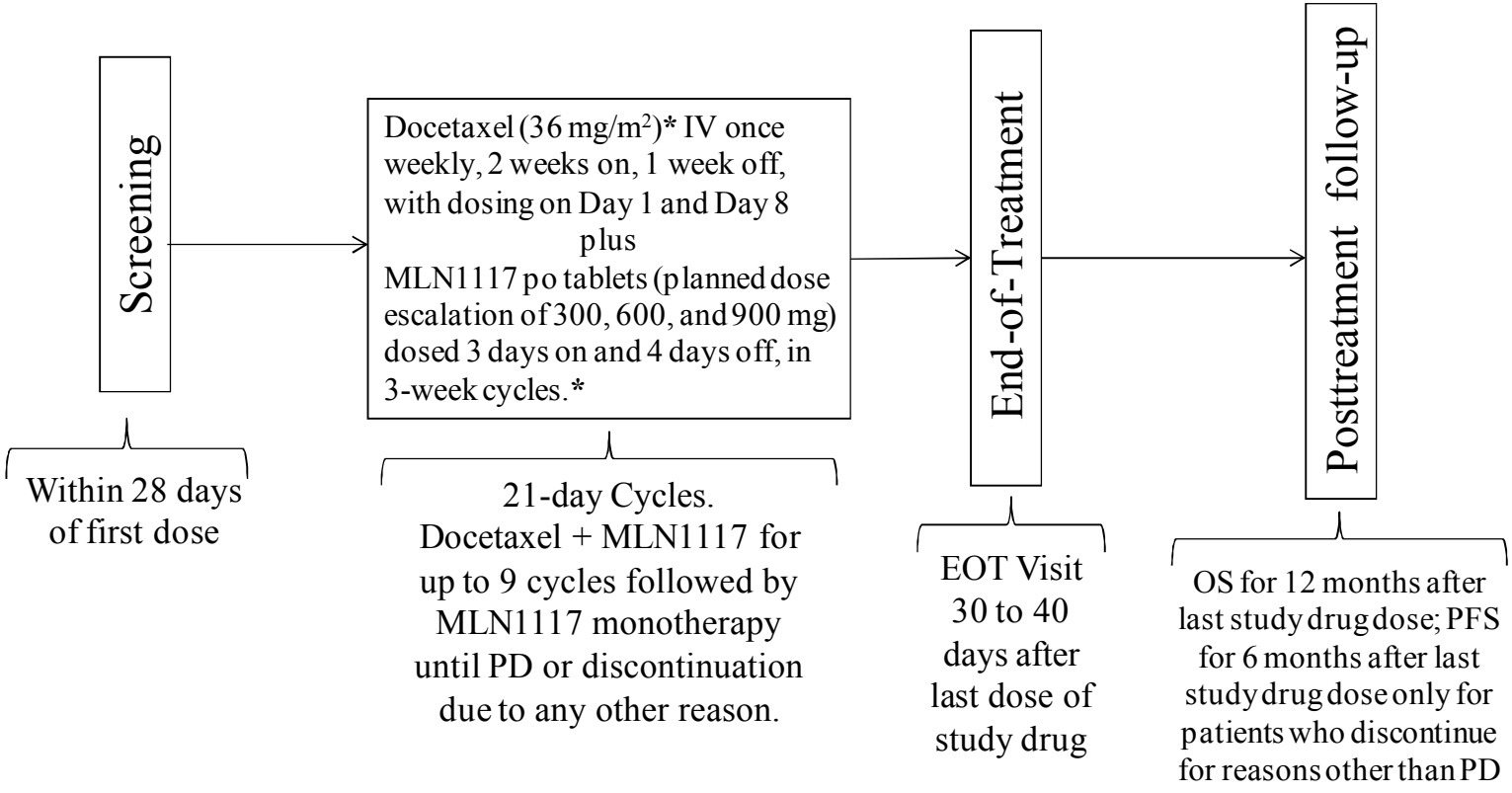
Study Population: The patient population will consist of adults 18 years of age or older with locally advanced or metastatic NSCLC refractory or resistant to 1 prior line of platinum-based, non-docetaxel-containing systemic chemotherapy (Phase 2). Also eligible for Phase 2 are patients who, after front-line, platinum-based, non-docetaxel-containing chemotherapy, received 1 line of nivolumab or other immune-checkpoint inhibitors but progressed on or after that therapy. Patients with NSCLC who have been treated with multiple prior lines of therapies are eligible for Phase 1b. Patients must have a histologically or cytologically confirmed diagnosis of NSCLC (squamous or nonsquamous). In Phase 2 of the study, patients with squamous NSCLC with a diagnosis of mixed squamous and nonsquamous (or adenosquamous) NSCLC are acceptable; patients with nonsquamous NSCLC with known driver mutations (*EGFR* and *ALK*) indicated for front-line targeted therapy are excluded as are patients with known *KRAS* gene mutations. Patients must have locally advanced or metastatic disease (Stage IIIb or Stage IV) with radiographically or clinically evaluable lesions per modified RECIST criteria (Version 1.1). Measurable disease by radiographic techniques (CT or MRI) is required only for Phase 2 of the study. Patients enrolled in Phase 2 must have archived or fresh tumor biopsy samples obtained during screening sufficient for genotyping; enrollment will be contingent on the local or central laboratory confirming receipt of an adequate amount of tissue including sufficient DNA for analysis. Patients must have adequate organ function and an Eastern Cooperative Oncology Group Performance Status of 0 or 1. Patients must have recovered (ie, ≤ Grade 1 toxicity or eligibility per this protocol is met) from the reversible effects of prior anticancer therapy. Patients who have been previously treated with a phosphoinositide 3-kinase or AKT inhibitor are not to be enrolled. No patients will have exposure to strong inhibitors or inducers of cytochrome P450 3A within 14 days, proton pump inhibitors within 7 days, or histamine-H_2 receptor antagonists or neutralizing antacids within 24 hours before the first dose of study drug. Patients with poorly controlled diabetes mellitus and clinically significant co-morbidities will not be enrolled.

Duration of Study: Approximately 24 to 36 months based on the sequential and adaptive design of Phase 2 of the study

STUDY DESIGN DIAGRAM

PHASE 1b

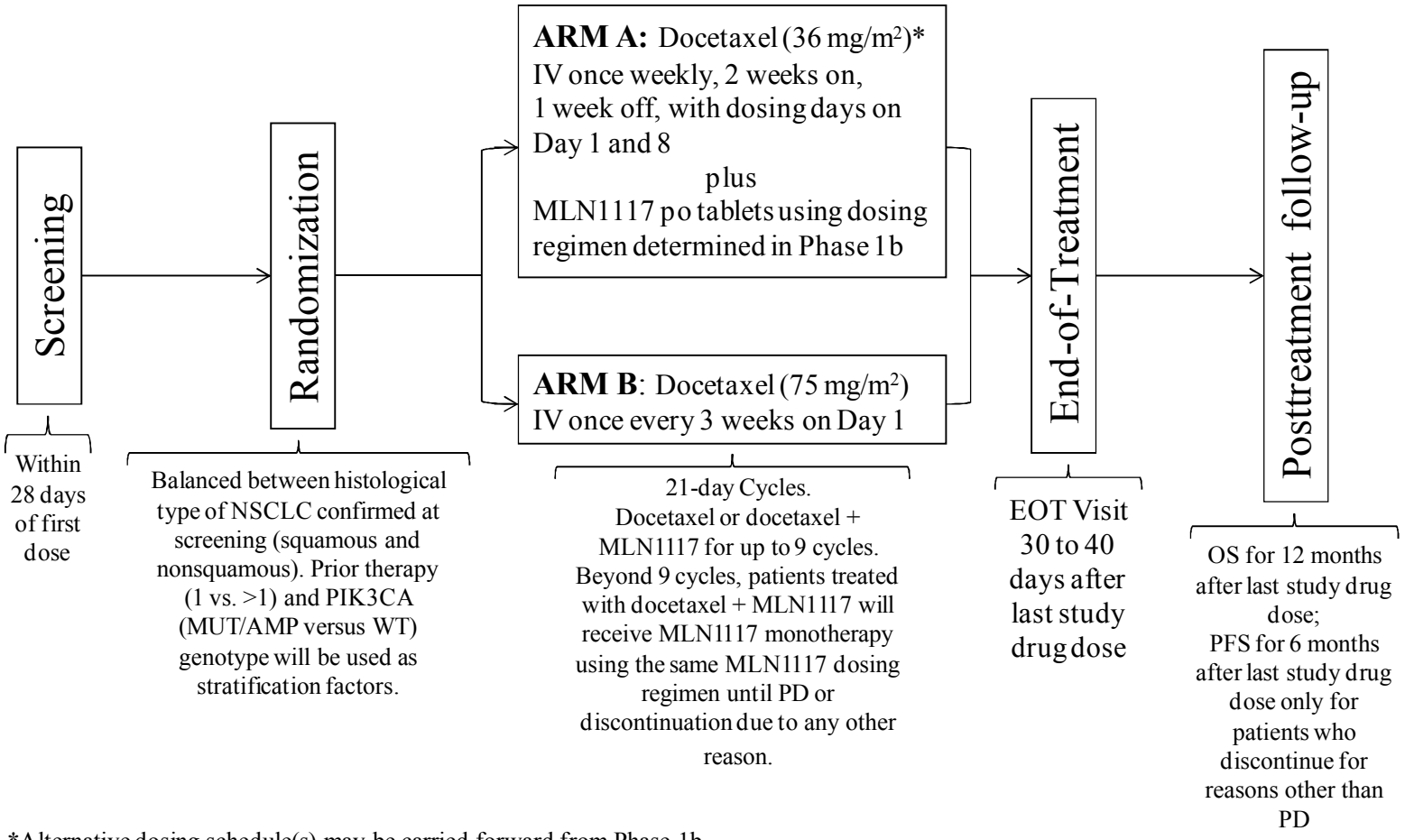
3 + 3 Dose Escalation: see Section 6.4 for dose escalation rules



*Alternative dosing schedule(s) may be investigated in Phase 1b and may be carried forward into Phase 2 of the study.

Abbreviations: EOT = end of treatment; IV = intravenous; OS = overall survival; PD = progressive disease; PFS = progression-free survival; po = by mouth.

PHASE 2



*Alternative dosing schedule(s) may be carried forward from Phase 1b.

Abbreviations: EOT= end of treatment; IV= intravenous; MUT/AMP = mutation and/or amplification; OS= overall survival; PD= progressive disease; PFS = progression-free survival; po = by mouth; WT = wildtype.

SCHEDULES OF EVENTS

	Screening[a] Within 28 Days	TREATMENT CYCLE 1						EOT[d]	PFSFUP/ OSFUP
		Day 1 Predose[a]	Day 2	Day 3[b]	Day 8	Day 9[c]	Day 16		
Informed consent[e]	X								
Inclusion/exclusion criteria	X								
Demographics	X								
Medical history	X								
Physical examination[f]	X	X	X	X	X	X	X	X	
Height	X								
Weight	X	X						X	
Vital signs[g]	X	X		X	X		X	X	
ECOG Performance Status	X	X						X	
Patient diary review		X	X		X	X	X	X	
[redacted]		X						X	
[redacted]		X						X	
12-lead ECG[i]	X	X	X			X		X	
Concomitant medications and procedures[j]		Recorded from the first dose through 30 days after the last dose							
AE collection		Recorded from the first dose through 30 days after the last dose							
SAE collection[k]	Recorded from the time the informed consent is signed through 30 days after the last dose of study drug								
Pregnancy test[l]	X	X							
Hematology[m]	X	X	X		X	X	X	X	
Chemistry[m]	X	X	X		X	X	X	X	
Urinalysis	X	X						X	
Fasting serum glucose[n]	X		X			X	X	X	
Fasting lipid profile[o]	X	X							

	Screening[a] Within 28 Days	TREATMENT CYCLE 1						EOT[d]	PFSFUP/ OSFUP
		Day 1 Predose[a]	Day 2	Day 3[b]	Day 8	Day 9[c]	Day 16		
HbA1c	X								
In-home daily fasting glucose monitoring		See footnote p							
Blood samples for PK		For Phase 1b, see the Plasma Pharmacokinetic Sampling Schedule During Phase 1b. For Phase 2, see the Plasma Pharmacokinetic Sampling Schedule During Phase 2, Arm A Only.							
Blood germline DNA	X								
Plasma ctDNA	X								
Tumor tissue (banked) or fresh biopsy sample[q]	X								
Disease evaluation by RECIST 1.1 (CT/MRI)[r]	X	Disease assessment to be conducted during Days 18-21 at the end of Cycles 2, 4, and 6 and then every 3 cycles thereafter							X Q2 mo
OS follow-up (OS and subsequent anticancer therapy)[s]									X Q3 mo
Dosing									
Phase 1b [t, u, v]		Docetaxel (36 mg/m^2) IV once weekly, 2 weeks on, 1 week off, in combination with MLN1117, 3 days on and 4 days off, for 3-week cycles for up to 9 cycles							
Phase 2 – Arm A[t, u, v]		Docetaxel (36 mg/m^2) IV once weekly, 2 weeks on, 1 week off, in combination with MLN1117 (dose TBD from dose escalation), 3 days on and 4 days off, for 3-week cycles for up to 9 cycles							
Phase 2 – Arm B[v]		Docetaxel (75 mg/m^2) IV once every 3 weeks							

Abbreviations: AE = adverse event; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] EOT = end of treatment; HbA1c = hemoglobin A1c; IV = intravenous(ly); mo = month(s); MRI = magnetic resonance imaging; OS = overall survival; OSFUP = overall survival follow-up; PFSFUP = progression-free survival follow-up; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TBD = to be determined.

	Screening[a] Within 28 Days	TREATMENT CYCLE 1						EOT[d]	PFSFUP/ OSFUP
		Day 1 Predose[a]	Day 2	Day 3[b]	Day 8	Day 9[c]	Day 16		

a Screening assessments are performed within 28 days before the Cycle 1 Day 1 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 Assessments on Day 3 will be done ONLY when patients are in the clinic for Phase 1b PK sampling, see Plasma Pharmacokinetic Sampling Schedule During Phase 1b.

c Phase 2, Arm B patients will not attend the Cycle 1 Day 9 visit.

d The EOT visit will occur 30-40 days after the last dose of study drug.

e Informed consent may be captured before the Screening period (28 days before Cycle 1 Day 1 dosing).

f A standard-of-care physical exam, including neurological assessment, should be done at screening, predose on Days 1, 2, 8, and 9; on Day 16 postdose; and at EOT. The physical exam on Days 2, 3, 8, 9, and 16 should be symptom directed.

g Vital signs should be obtained at screening, predose on Days 1 and 8; and on Day 16 postdose; and at EOT. Vital signs include blood pressure, heart rate, and temperature.

h On Day 1 only of every cycle and at EOT (Phase 2, only).

i Single 12-lead ECGs will be conducted at Screening, on Cycle 1 Day 1 predose; Cycle 1 Day 2 predose and at 4 hours (± 30 min) post MLN1117 dose; Cycle 1 Day 9 predose; and at EOT. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, then the ECG will be completed before the collection of the blood sample.

j See Section 6.6 for medications and procedures that are prohibited during the study and Section 6.8 for medications that should be used cautiously during the study.

k Only those SAEs that occur after the first dose of study drug will be collected in the electronic case report form; however, all SAEs occurring after consent will be reported. See Section 9.

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

m Samples may be collected up to 3 days before the scheduled visit. See Section 7.4.13 for the full hematology and chemistry panel.

n Phase 1b fasting serum glucose will be measured at screening; Cycle 1 Day 2 predose and at 0.5 hours (± 15 min), 1 hour (± 15 min), 2 hours (± 30 min), 4 hours ([± 30 min] fasting not required), 8 hours ([± 30 min] fasting not required), and 24 hours (± 2 hours) after dosing; Cycle 1 Day 9 predose and 2 hours (± 30 min) postdose; Cycle 1 Day 16 predose only; and at EOT. Phase 2 fasting serum glucose will be measured at screening; Cycle 1 Day 2 predose; Cycle 1 Day 9 predose; and at EOT.

o See Section 7.4.13 for the fasting lipid panel.

p Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥ 140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 7.4.15 for further instruction.

	Screening[a] Within 28 Days	TREATMENT CYCLE 1						EOT[d]	PFSFUP/ OSFUP
		Day 1 Predose[a]	Day 2	Day 3[b]	Day 8	Day 9[c]	Day 16		

q Tumor tissue (banked) will be required at screening as specified in Section 7.4.17. For banked tissue, the sample can be from either paraffin-embedded tumor block or unstained slides. If a paraffin-embedded tumor block or unstained slides are not available, the patient will be required to undergo a fresh tumor biopsy as specified in Section 7.4.17. The sample must be collected during screening before the first dose of study drug. Tumor tissue will be analyzed and will be tested retrospectively for genetic mutations and amplifications.

r Response assessments will be performed on Days 18-21 at the end of treatment Cycles 2, 4, and 6 and then every 3 cycles thereafter starting at Cycle 9 until the patient discontinues study drug due to disease progression, unacceptable toxicity, or death. A CT scan with IV contrast of the chest, abdomen, and pelvis will be performed during screening (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study). If the patient has had an appropriate CT or MRI scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening. For patients who discontinue for reasons other than disease progression, PFS is to be assessed every 2 months up to 6 months after study treatment.

s OS is to be assessed every 3 months for up to 1 year after the patient's last dose of study drug.

t Patients will be treated for up to 9 cycles with either docetaxel alone or docetaxel plus MLN1117. Patients receiving docetaxel plus MLN1117 will continue treatment with MLN1117 monotherapy beyond Cycle 9.

u During Phase 1b, if MLN1117 de-escalation is warranted, the daily dose of MLN1117 may be reduced or the number of treatment days per week may be reduced (eg, from 3 days to 2 days, or further to 1◦day); see Section 6.1 for details.

v Testing of escalating MLN1117 doses in combination with a fixed docetaxel dose and schedule is planned. However, if frequent docetaxel dose modifications are necessary when administered in combination with MLN1117, the fixed dose of docetaxel may be decreased (eg, –1 dose level) based on discussion and agreement between investigators and the Millennium project clinician; see Section 6.1.

	TREATMENT CYCLES 2-9		EOT[a]	PFSFUP/ OSFUP
	Day 1	Day 8		
Physical examination[b]	X	X[b]	X	
Weight	X		X	
Vital signs[c]	X	X	X	
ECOG Performance Status	X		X	
Patient Diary Review	X	X	X	
[redacted]	X		X	
[redacted]	X		X	
12-lead ECG[e]	X		X	
Concomitant medications and procedures[f]	Recorded from the first dose through 30 days after the last dose			
AE collection	Recorded from the first dose through 30 days after the last dose			
SAE collection[g]	Recorded from the time the informed consent is signed through 30 days after the last dose of study drug			
Pregnancy test[h]	X			
Hematology[i]	X	X	X	
Chemistry[i]	X	X	X	
Urinalysis	X		X	
Fasting serum glucose[j]	X	X	X	
Fasting lipid profile[k]	X			
In-home daily fasting glucose monitoring	See footnote l.			
Plasma ctDNA[m]	X			
Disease evaluation by RECIST 1.1 (CT/MRI)[n]	Disease assessment to be conducted during Days 18-21 at the end of the end of Cycles 2, 4, and 6 and then every 3 cycles thereafter			X Q2 mo
OS follow-up (OS and subsequent anticancer therapy) [o]				X Q3 mo

	TREATMENT CYCLES 2-9		EOT[a]	PFSFUP/ OSFUP
	Day 1	Day 8		
Dosing				
Phase 1b [p, q, r]	Docetaxel (36 mg/m^2) IV once weekly, 2 weeks on, 1 week off, in combination with MLN1117, 3 days on and 4 days off, for 3-week cycles for up to 9 cycles			
Phase 2 – Arm A[p, q, r]	Docetaxel (36 mg/m^2) IV once weekly, 2 weeks on, 1 week off, in combination with MLN1117 (dose TBD from dose escalation), 3 days on and 4 days off, for 3-week cycles for up to 9 cycles			
Phase 2 – Arm B[r]	Docetaxel (75 mg/m^2) IV once every 3 weeks			

Abbreviations: AE = adverse event; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] EOT = end of treatment; IV = intravenous(ly); mo = month(s); MRI = magnetic resonance imaging; OS = overall survival; OSFUP = overall-survival follow-up; PFSFUP = progression-free survival follow-up; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a The EOT visit will occur 30-40 days after the last dose of study drug.

b A standard-of-care physical exam, including neurological assessment, should be done predose on Day 1 and Day 8, and at EOT. The physical exam on Day 8 should be symptom directed.

c Vital signs should be obtained predose on Day 1 and Day 8 and at EOT. Vital signs include blood pressure, heart rate, and temperature.

d On Day 1 only of every cycle and at EOT (Phase 2 only).

e ECGs should be taken predose on Day 1 of every cycle and at EOT. When the timing of a safety laboratory blood sample coincides with the timing of ECG measurements, then the ECG will be completed before the collection of the blood sample.

f See Section 6.6 for medications and procedures that are prohibited during the study and Section 6.7 for medications that should be used cautiously during the study.

g Only those SAEs that occur after the first dose of study drug will be collected in the electronic case report form; however, all SAEs occurring after consent will be reported. See Section 9.

h Urine pregnancy test must be performed before Day 1 of each cycle.

i Samples may be collected up to 3 days before the scheduled visit. See Section 7.4.13 for the full hematology and chemistry panel.

j Fasting serum glucose (FSG) is required on Day 1 predose and Day 8 predose for Cycles 2-9 and at EOT.

k See Section 7.4.13 for the fasting lipid panel.

l Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥ 140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 7.4.15 for further instruction.

	TREATMENT CYCLES 2-9			
	Day 1	Day 8	EOT[a]	PFSFUP/ OSFUP

m Samples to be taken on Day 1 every 2 cycles, starting at Cycle 3 Day 1, until EOT.

n Response assessments will be performed on Days 18-21 at the end of treatment Cycles 2, 4, and 6 and then every 3 cycles thereafter starting at Cycle 9 until the patient discontinues study drug due to disease progression, unacceptable toxicity, or death. A CT scan with IV contrast of the chest, abdomen, and pelvis will be performed during screening (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study). If the patient has had an appropriate CT or MRI scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening. For patients who discontinue for reasons other than disease progression, PFS is to be assessed every 2 months up to 6 months after study treatment.

o OS is to be assessed every 3 months for up to 1 year after the patient's last dose of study drug.

p Patients will be treated for up to 9 cycles with either docetaxel alone or docetaxel plus MLN1117. Patients receiving docetaxel plus MLN1117 will continue treatment with MLN1117 monotherapy beyond Cycle 9.

q During Phase 1b, if MLN1117 de-escalation is warranted, the daily dose of MLN1117 may be reduced or the number of treatment days per week may be reduced (eg, from 3 days to 2 days, or further to 1◦day; see Section 6.1 for details.

r Testing of escalating MLN1117 doses in combination with a fixed docetaxel dose and schedule is planned. However, if frequent docetaxel dose modifications are necessary when administered in combination with MLN1117, the fixed dose of docetaxel may be decreased (eg, –1 dose level) based on discussion and agreement between investigators and the Millennium project clinician; see Section 6.1.

	TREATMENT CYCLES 10 AND BEYOND (for Single-Agent MLN1117 ONLY)		
	Predose Day 1 or 2	**EOT[a]**	**PFSFUP/ OSFUP**
Physical examination	X	X	
Weight	X	X	
Vital signs[b]	X	X	
ECOG Performance Status	X	X	
Patient diary review	X	X	
[redacted]	X	X	
[redacted]	X	X	
12-lead ECG[d]	X[d]	X	
Concomitant medications and procedures[e]	Recorded from the first dose through 30 days after the last dose		
AE collection	Recorded from the first dose through 30 days after the last dose		
SAE collection[f]	Recorded from the time the informed consent is signed through 30 days after the last dose of study drug		
Pregnancy test[g]	X		
Hematology[h]	X	X	
Chemistry[h]	X	X	
Urinalysis	X	X	
Fasting serum glucose	X	X	
Fasting lipid profile[i]	X		
In-home daily fasting glucose monitoring[j]	See footnote j.		
Plasma ctDNA [k]	X		
Disease evaluation by RECIST 1.1 (CT/MRI)[l]	Disease assessment to be conducted during Days 18-21 at the end of the end of Cycles 2, 4, and 6 and then every 3 cycles thereafter		X Q2mo
OS follow-up (OS and subsequent anticancer therapy)[m]			X Q3mo

	TREATMENT CYCLES 10 AND BEYOND (for Single-Agent MLN1117 ONLY)	EOT[a]	PFSFUP/ OSFUP
	Predose Day 1 or 2		
Dosing			
Phase 1b[n]	MLN1117 (dose TBD from dose escalation), 3 days on and 4 days off, for 3-week cycles		
Phase 2 – Arm A[n]	MLN1117 (dose TBD from dose escalation), 3 days on and 4 days off, for 3-week cycles		

Abbreviations: AE = adverse event; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted]; EOT = end of treatment; MRI = magnetic resonance imaging; OS = overall survival; OSFUP = overall-survival follow-up; PFSFUP = progression-free survival followup; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TBD = to be determined.

a The EOT visit will occur 30-40 days after the last dose of study drug.

b Vital signs should be assessed predose on Day 1 or Day 2, and at EOT. Vital signs include blood pressure, heart rate, and temperature.

c On Day 1 or 2 of every cycle and at EOT (Phase 2 only).

d ECGs should be taken predose on Day 1 or Day 2 of every cycle and at EOT.

e See Section 6.6 for medications and procedures that are prohibited during the study and Section 6.8 for medications that should be used cautiously during the study.

f Only those SAEs that occur after the first dose of study drug will be collected in the electronic case report form; however, all SAEs occurring after consent will be reported. See Section 9.

g Urine pregnancy test must be performed before Day 1 or Day 2 of each cycle.

h Samples may be collected 3 days before the scheduled visit. See Section 7.4.13 for the full hematology and chemistry panel.

i See Section 7.4.13 for the fasting lipid panel.

j Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥ 140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 7.4.15 for further instruction.

k Samples to be taken on Day 1 or Day 2 every 2 cycles, starting at Cycle 11 Day 1, until EOT.

l Response assessments will be performed on Days 18-21 at the end of treatment Cycles 2, 4, and 6 and then every 3 cycles thereafter starting at Cycle 9 until the patient discontinues study drug due to disease progression, unacceptable toxicity, or death. A CT scan with intravenous contrast of the chest, abdomen, and pelvis will be performed during screening (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study). If the patient has had an appropriate CT or MRI scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening. For patients who discontinue for reasons other than disease progression, PFS to be assessed every 2 months up to 6 months after study treatment.

m OS is to be assessed every 3 months for up to 1 year after the patient's last dose of study drug.

	TREATMENT CYCLES 10 AND BEYOND (for Single-Agent MLN1117 ONLY)		
	Predose Day 1 or 2	EOT[a]	PFSFUP/ OSFUP

n During Phase 1b, if MLN1117 de-escalation is warranted, the daily dose of MLN1117 may be reduced or the number of treatment days per week may be reduced (eg, from 3 days to 2 days, or further to 1◦day). See Section 6.1 for details.

PHARMACOKINETIC SAMPLING SCHEDULES

Plasma Pharmacokinetic Sampling Schedule During Phase 1b

	Cycle 1
Time Point	**Day 2**
Predose; within 30 min of dosing	X
0.5 hours postdose (± 5 min)	X
1 hour postdose (± 15 min)	X
2 hours postdose (± 15 min)	X
4 hours postdose (± 45 min)	X
6 hours postdose (± 45 min)	X
8 hours postdose (± 1 h)	X
24 hours postdose (± 1 h)	X
Total Samples	**8**

Plasma Pharmacokinetic Sampling Schedule During Phase 2, Arm A Only

	Cycle 1	Cycle 1
Time Point	**Day 2**	**Day 16**
At time of clinic visit (2-6 hours postdose)[a]		X
Approximately 1 hour after the last PK sample (3-7 hours postdose)[a]		X
Predose; within 30 min of dosing	X	
0.5 hours postdose (± 5 min)	X	
1 hour postdose (± 15 min)	X	
2 hours postdose (± 15 min)	X	
4 hours postdose (± 45 min)	X	
Total Samples	**5**	**2**

a On Cycle 1 Day 16 patients will take their MLN1117 dose at home and report to the clinical site 2-6 hours after dosing.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT3	5-hydroxytryptamine
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	aspartate aminotransferase
ATP	adenosine 5' triphosphate
AUC	area under the plasma concentration versus time curve
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{last}	area under the plasma concentration versus time curve from zero to the time of the last quantifiable concentration
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
BID	*bis in die*; twice daily
BUN	blood urea nitrogen
CI	confidence interval
CL/F	apparent total body clearance

Abbreviation	Term
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
[redacted]	[redacted]
[redacted]	[redacted]
EOT	End of Treatment (visit)
FBG	fasting blood glucose
FSG	fasting serum glucose
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
hCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor 2
$HR_{MUT/AMP}$	squamous *PIK3CA* mutation and/or amplification hazard ratio
$HR_{nonsquamous}$	nonsquamous hazard ratio
$HR_{overall}$	overall hazard ratio
[redacted]	[redacted]

Abbreviation	Term
$HR_{squamous}$	squamous hazard ratio
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IGFR	insulin-like growth factor receptor
ITT	intent-to-treat
IV	intravenous; intravenously
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test(s)
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MLN1117	TAK-117
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTORr	serine/threonine kinase mechanistic target of rapamycin
MTW	Monday, Tuesday, and Wednesday
MUT/AMP	mutation and/or amplification
MWF	Monday, Wednesday, and Friday
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
OCT	organic cation transporter
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression-free survival
Pgp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PI3Kα	phosphoinositide 3-kinase alpha isoform
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PTEN	phosphatase and tensin homolog

Abbreviation	Term
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
QD	*quaque die*; once daily
QW	weekly
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RR	response rate
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal disposition half-life
TAK-117	MLN1117
TEAE	treatment-emergent adverse event
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
TTP	time to progression
ULN	upper limit of the normal range
US	United States
USPI	United States Prescribing Information
WT	wild-type

1. BACKGROUND AND STUDY RATIONALE

MLN1117 is an orally available, potent, and selective small molecule inhibitor of the class I phosphoinositide 3-kinase (PI3K) alpha isoform (PI3Kα). It is being developed for the treatment of malignancies in which the PI3K pathway is believed to contribute significantly to the pathologic process and response to the standard therapies.

MLN1117 is also being developed in combination with MLN0128 (a novel, highly selective, orally bioavailable adenosine 5' triphosphate (ATP)-competitive inhibitor of the serine/threonine kinase referred to as the metabolic target of rapamycin [mTORr]) as a treatment for advanced nonhematologic malignancies.

1.1 Disease Under Treatment

Lung cancer, classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), remains the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer, including squamous cell carcinoma and nonsquamous cell carcinoma (adenocarcinoma, large cell carcinoma, and others), accounts for more than 80% of all lung cancer cases. The majority of patients with NSCLC are diagnosed at an advanced stage with inoperable, locally advanced or metastatic disease. Therefore, the standard treatment, which commonly includes a combination of chemotherapy and radiation therapy, focuses mainly on disease control and maintenance of quality of life. The overall survival (OS) for patients with NSCLC in the advanced setting is approximately 8 to 10 months, making it an area of highly unmet medical need that attracts extensive research and development efforts.[4]

1.2 MLN1117

Activating somatic missense mutations (eg, E542K, E545K, and H1047R) in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) gene encoding the p110α catalytic subunit of PI3Kα have been identified as a major mechanism for PI3K-dependent malignant transformation, proliferation, and survival. *PIK3CA* mutations have been reported to occur in various solid tumors with the highest rates in breast (27%), endometrial (24%), bladder (23%), colon (15%), and ovarian (10%) cancers.[5, 6, 7] In addition to direct mutations of PI3Kα, the pathway may also be activated by mutations or overexpression of upstream effectors such as receptor tyrosine kinases (RTKs) including human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), and insulin-like growth factor receptor (IGFR). *PIK3CA* is also amplified in several tumor types including the squamous type of NSCLC.[8] MLN1117 is a selective,

small molecule inhibitor of PI3K. MLN1117 has demonstrated greatest antiproliferative activity in cell lines harboring *PIK3CA* activating mutations and/or HER2 overexpression.

1.2.1 Nonclinical Experience

In human tumor mouse xenograft models harboring activating mutations for PI3Kα, MLN1117 inhibited pharmacodynamic markers of the PI3K pathway that correlate with strong tumor growth inhibition in a specific and dose-dependent manner.

Secondary pharmacology studies demonstrated no appreciable off-target activities and limited potential to affect metabolism or immune function at pharmacologically active doses and exposures.

MLN1117 displayed no effect on electrocardiograms (ECGs) obtained from monkeys and low potential concentration required for 50% inhibition effect (IC_{50}) > 30 μM to affect the human ether-a-go-go-related potassium channel.

MLN1117 displayed consistent and predictable oral (PO) pharmacokinetic (PK) parameters across mice, rats, and monkeys, with rapid absorption first time to maximum plasma concentration (T_{max}) (ranging from 0.25-5.0 hours) and high PO bioavailability (ranging from 70%-98%). Pharmacokinetic analysis displayed a dose-dependent increase in MLN1117 levels in plasma and tumor lysates in the MDA-MB-453 tumor xenograft model. MLN1117 is also an inhibitor of organic cation transporter (OCT)1, OCT2, and breast cancer resistance protein (BCRP), but not of P-glycoprotein (Pgp). Multiple human cytochrome P450 (CYP) isozymes (CYP3A4/5, 1A2, 2C8, and 2C9) appear to contribute to MLN1117 metabolism, with CYP3A4 responsible for 72% of the metabolism, when normalized for liver content. MLN1117 displayed low potential (IC_{50} > 100 μM) for inhibition of CYP3A4/5, CYP2D6, CYP2C19, CYP2C9, CYP2C8, and CYP1A2, and did not induce CYP1A2, 2B6, or 3A4/5 activity, except in 1 hepatocyte preparation, in which there was an increase in CYP3A4 mRNA; however, this was not associated with an increase in CYP3A4/5 activity. The potential for MLN1117 to cause exposure changes to concomitantly administered CYP isozyme substrates is low; however, concomitantly administered inhibitors and inducers of CYP3A4 isozyme can affect the exposure to MLN1117.

Toxicology studies were performed in rats and in monkeys. After repeat PO administration in the rat, doses ≤ 100 mg/kg were well tolerated, and a dose of 300 mg/kg was considered severely toxic. Twenty-eight days of repeat PO dosing in the monkey demonstrated that

doses ≤ 50 mg/kg were well tolerated, and a dose of 250 mg/kg produced dose-limiting and severe toxicities. The observed toxicities were consistent between rats and monkeys with no apparent sex differences.

The adverse effects observed in rats included decreases in body weight and test article-related alterations primarily centered on minimal to mild lymphoid depletion that correlated with clinical pathology, organ weight, and microscopic observations including lower white blood cell and lymphocyte counts; decreased spleen and thymus weights, and lymphoid depletion in multiple lymph nodes, Peyer's patches, spleen, and thymus; bone marrow depletion; and decreased incidence/severity of background mononuclear infiltrates in the liver. In the monkey, test-article related alterations were limited to lymphoid depletion and included decreased thymus weights and minimal to mild microscopic lymphoid depletion in the thymus, spleen, and 1 or more lymph nodes.

On the basis of 28-day Good Laboratory Practice (GLP) toxicology studies, the severely toxic dose in 10% in rats was 100 mg/kg (600 mg/m^2) and the highest nonseverely toxic dose in monkeys was 50 mg/kg (600 mg/m^2).

MLN1117 was evaluated in the bacterial reverse mutation (Ames) assay, and there was no evidence of mutagenicity.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN1117 may be found in the Investigator's Brochure (IB).

1.2.2 Clinical Experience

Millennium is currently evaluating the safety, tolerability, and PK profile of single-agent MLN1117 in a first-in-human, dose-finding study in patients with advanced, nonhematologic malignancies (Study INK1117-001). This ongoing phase 1 study is designed to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) and dose-limiting toxicities (DLTs) when MLN1117 is administered PO on 21-day cycles of daily and intermittent dosing schedules. Study INK1117-001 consists of a dose escalation phase and a dose-level expansion phase. The escalation phase will enroll approximately 120 patients with any solid tumor. The expansion phase will enroll approximately 70 patients who have breast cancer or non-small cell lung cancer. As of 23 June 2014, a total of 78 patients had been enrolled into the escalation phase and had received at least 1 dose of MLN1117. A tabular summary of the weekly dosing regimens administered as of 23 June 2014 is presented in Table 1.a.

Table 1.a INK1117-001 Dosing Regimens

Weekly Dosing Regimen/Dose (mg)	No. of Subjects
QD: 100, 150, 200, 300 QD on MWF QW: 200, 300, 400, 600, 900, 1200 QD on MTW QW: 200, 400, 600, 900 BID on MWF QW: 300	Enrolled: 78

Abbreviations: BID = twice daily; MTW = Monday, Tuesday, and Wednesday; MWF = Monday, Wednesday, and Friday; QD = once daily; QW = each week.

In the PK analysis portion of this study, MLN1117 capsules were administered PO using 3 different dosing schedules: once daily (QD); 3 days each week (QW) of consecutive-day dosing (eg, Monday, Tuesday, and Wednesday [MTW] QW); and 3 days each week of every-other-day dosing (eg, Monday, Wednesday, and Friday [MWF] QW). The plasma PK of MLN1117 was evaluated in Study INK1117-001 for 24 hours after dosing of MLN1117 on Day 1 of Cycles 1 and 2, and during Week 2 of Cycle 1. Preliminary PK data suggest fast PO absorption following MLN1117 dosing, with a mean plasma terminal disposition half-life ($t_{½}$) of approximately 11 hours across cohorts. The extent of accumulation following QD dosing was low (accumulation ratio of approximately 1.2). Systemic exposures of MLN1117 increased with increasing dose over the 100- to 1200-mg dose range. There was a 9-fold increase in plasma exposure (area under the plasma concentration versus time curve [AUC] from zero to infinity [AUC_{inf}]) of MLN1117, with a 12-fold increase in dose from 100 to 1200 mg.

Of the 78 patients treated in Study INK1117-001 for whom data had been entered into the clinical database as of the data cutoff, 75 (96%) had reported ≥ 1 treatment-emergent adverse event (TEAE), and 67 patients (86%) had experienced ≥ 1 TEAE that was considered to be study drug related. The most commonly reported (≥ 15% of patients overall) study drug-related adverse events (AEs) included nausea (36 patients, 46%), hyperglycemia or vomiting (25 patients each, 32%), diarrhea (22 patients, 28%), fatigue (18 patients, 23%), aspartate aminotransferase (AST) increased or appetite decreased (15 patients each, 19%), and alanine aminotransferase (ALT) increased (12 patients, 15%). Adverse events with severity ≥ Grade 3 were reported in 38 of 78 patients (49%). The most common (≥ 5% of patients) ≥ Grade 3 AEs that were reported as being related to MLN1117 were ALT increased (6 patients, 8%), hyperglycemia (5 patients, 6%), and AST increased (4 patients, 5%).

Of 23 patients treated with QD MLN1117 on [MTW] QW, the regimen of MLN1117 that will be used in this study, the most commonly reported (≥ 10% of patients) study drug-related AEs were nausea (11 patients, 48%), hyperglycemia or vomiting (9 patients each, 39%), diarrhea or fatigue (7 patients each, 30%), AST increased or asthenia (3 patients each, 13%). The ≥ Grade 3 study drug-related AEs associated with the [MTW] QW schedule include hyperglycemia (3 patients, 13%) and ALT increased (1 patient, 4%). No ≥ Grade 3 drug-related AST increased was observed in the [MTW] QW cohort.

A total of 11 patients (14%) had discontinued from Study INK1117-001 because of 1 or more AEs as of the clinical data cutoff; most events were reported as severity Grade 3, and the majority were considered not related to study drug. No events of severity Grade 4 were reported as resulting in study discontinuation, although 2 events (hypercalcemia, respiratory failure) resulted in fatal outcomes; neither of these events was considered related to study drug.

As of the clinical data cutoff, serious adverse events (SAEs) had occurred in 29 of the 78 enrolled patients (37%) in Study INK1117-0001. The majority of the SAEs were reported as unrelated to study drug and resolved without sequelae. A total of 6 patients had died either during the treatment period or within 30 days of their last dose of study drug; none of the fatalities were considered related to study drug.

Millennium has also initiated a multicenter, open-label, phase 1b trial (C32001) of MLN1117 in combination with MLN0128 (a PO mTORC1/2 inhibitor) administered to adult patients with advanced nonhematologic malignancies. The primary objective of this study is to evaluate the safety, tolerability, PK, and pharmacodynamics of MLN0128 in combination with MLN1117.

Further details on these studies are provided in the IB.

1.3 Docetaxel

Docetaxel is an antimicrotubule agent that has demonstrated significant clinical activity both as single-agent therapy and in combination with other chemotherapeutic agents in a wide range of solid tumors. In the United States (US) and Europe, docetaxel is approved as single-agent therapy for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC. Investigators are instructed to consult the most recent local prescribing information

(eg, SmPC, USPI, etc) for complete details regarding the administration and management of docetaxel.

1.4 Study Rationale

The PI3K signaling pathway critical for many cellular processes, such as proliferation and survival, is frequently dysregulated in lung cancer in response to genetic alterations that affect one of its components: activating mutations or amplification of upstream receptor tyrosine kinase, amplification of PI3K, loss or inactivation of PTEN, over-activation of downstream kinase AKT, and mutational activation of the *PIK3CA* gene encoding the p110α catalytic subunit of PI3K. Activating mutations of *PIK3CA* have been found in approximately 5% to 10% of NSCLC; however, genomic amplification of *PIK3CA* was identified in 30% to 50% of squamous cell carcinoma of lung. Chemotherapy is also known to cause activation of the PI3K pathway in cancer cells to sustain survival.[9] Nonclinical pharmacology data demonstrated significant antitumor activity in xenograft models of NSCLC, in particular, in combination with docetaxel. Therefore, targeting PI3K signaling, particularly by a PI3Kα-specific inhibitor such as MLN1117, may provide a potential treatment option for patients with advanced NSCLC in combination with standard care agents such as docetaxel.

1.4.1 Rationale for Combining MLN1117 With Docetaxel

Preliminary nonclinical evaluation of MLN1117 in combination with docetaxel, a standard chemotherapy agent commonly used in both the front-line (in combination with other chemotherapy agents) and second-line (single agent) or later settings, demonstrated equal or better antitumor activity when MLN1117 was administered 24 hours after treatment with docetaxel compared with concomitant dosing of both compounds in a small cell lung carcinoma model using NCI-H1048 (NCDS-02264: Antitumor Activity of MLN1117 and Taxotere Alone or In Combination in NCI-H1048 Xenografts, and NCDS-02265: Scheduling Effect of MLN1117 in Combination with High Dose Taxotere on Tumor Growth Delay of NCI-H1048 Xenografts). In addition, treatment with docetaxel activated the PI3K pathway, which could be suppressed by MLN1117 resulting in enhanced apoptosis (NCDS-02263: PD [Pharmacodynamic] Evaluation of the Combination of Docetaxel and MLN1117 in NCI-H1048 Cells In Vitro). The current study is designed to clinically evaluate the combination of MLN1117 and docetaxel for safety, tolerability, optimal dose/schedule, and preliminary efficacy in advanced NSCLC.

1.4.2 Rationale for MLN1117 Dose and Schedule Selection

MLN1117 has been studied in a number of doses/schedules in Study INK1117-001 including QD, QD continuously on 3 days with 4 days off each week (ie, once-daily on MTW of each week), QD on 3 days with dosing on every other day of each week (ie, MWF of each week), and twice-daily (BID) on MWF of each week. Currently the highest tolerated dose of single-agent MLN1117 is 900 mg in both the MTW and MWF dosing schedules. Safety findings of these 2 schedules across dose levels that have been evaluated were comparable. Both schedules, at a given dose, deliver the same total weekly dose and comparable total weekly AUC of MLN1117. Because MLN1117 exhibits AUC-dependent efficacy in nonclinical efficacy studies, either MTW or MWF schedules are expected to provide comparable effect at similar doses of MLN1117. In this study, the MTW dosing schedule of 3 days continuous dosing with 4 days off each week will be selected to be combined with docetaxel. On the basis of nonclinical observations indicating better antitumor activity using sequential dosing of MLN1117 following docetaxel treatment, MLN1117 will be dosed 24 hours after docetaxel (see Section 1.4.1). Thus, MLN1117 will be dosed QD on Days 2 through 4, 9 through 11, and 16 through 18 of each dosing cycle. However, during Phase 1b, if MLN1117 de-escalation is warranted, the daily dose of MLN1117 may be reduced, or the number of treatment days per week may be reduced (eg, from 3 days to 2 days, or further to 1◦day); see Section 6.1. These decisions will be made jointly by investigators and the Millennium project clinician. The alternative MLN1117 regimen may be carried forward into Phase 2 of the study if deemed appropriate by the sponsor in consultation with the investigators.

The Phase 1b portion of the study is a dose escalation of MLN1117 in combination with docetaxel. This portion of the study will evaluate the safety, tolerability, and PK of MLN1117 administration at ascending dose levels (dose levels of 300, 600, and 900 mg are planned). MLN1117 doses will be administered 24 hours after docetaxel. The highest dose of MLN1117 that can be safely combined with docetaxel will be selected for the Phase 2 portion of the study.

1.4.3 Rationale for Docetaxel Dose Selection

For treatment after failure of prior platinum-based chemotherapy, the standard dose of docetaxel as monotherapy is 75 mg/m^2 administered intravenously (IV) over 1 hour every 3 weeks (Q3W). In this study, the docetaxel alone control arm will use this standard Q3W regimen. In the MLN1117 plus docetaxel arm, docetaxel will be administered on a weekly schedule at a dose of 36 mg/m^2 (2 weeks on, 1 week off) in combination with MLN1117. If,

however, during the dose-escalation phase, frequent docetaxel dose modifications are necessary, the fixed dose of docetaxel may be decreased (eg, –1 dose level) based on discussion and agreement between investigators and the Millennium project clinician. If decreased, the lower docetaxel dose may be carried forward into Phase 2 of the study if deemed appropriate by the sponsor in consultation with the investigators.

Administering docetaxel weekly has shown similar efficacy but better tolerability in a meta-analysis of 5 randomized trials comparing the weekly versus the Q3W regimen of docetaxel.[10] The weekly rather than the Q3W schedule of docetaxel has been selected in this study as it is best suited to combine with the 3-on/4-off weekly intermittent dosing regimen of MLN1117. Such a combination will provide 3 instances of combined dosing within a treatment cycle, where a 3-day pulse of MLN1117 would be administered 24 hours after each docetaxel dose to maximize the expected benefits from the combination anticipated from the previously described mechanistic studies and nonclinical data. The total docetaxel dose per cycle planned for the MLN1117 plus docetaxel arm (2×36 mg/m^2) is similar to that of the docetaxel alone control arm (75 mg/m^2).

This study is designed to clinically evaluate the combination of MLN1117 and docetaxel for safety, tolerability, optimal dose/schedule, and preliminary efficacy in advanced NSCLC.

1.5 Potential Risks and Benefits

MLN1117 is a selective inhibitor of PI3Kα that might provide a better tolerability profile than pan-PI3K inhibitors.

Grade 1 through 3 increases in ALT and/or AST have been observed in patients receiving MLN1117 in Study INK1117-001. The elevations were reported primarily in connection with the 200- and 300-mg QD doses. Most were nonserious and reversible. Patients in the current study will have frequent monitoring of liver function tests (LFTs) as outlined in the Schedules of Events.

Grade 1 through 3 hyperglycemia events have been reported in patients receiving MLN1117 in Study INK1117-001. Elevations were minimized with antihyperglycemic agents or no intervention. In addition to obtaining fasting serum glucose (FSG) levels at the study site (see Schedules of Events), patients in this study who experience hyperglycemia will be given a glucometer 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 for further instructions on the management of their hyperglycemia.

Nausea and vomiting have been reported among the most frequent drug-related AEs in patients receiving MLN1117 in Study INK1117-001. Use of anti-emetics (such as PO compazine or ondanestron) per local standard care, if needed to control nausea or vomiting, is permitted.

Further details regarding TEAEs observed in patients receiving MLN1117 in Study INK1117-001 are presented in the MLN1117 IB.

Please refer to Section 6.9 for instructions regarding the management of these AEs.

Patients treated with docetaxel commonly experience bone marrow suppression, gastrointestinal events, fatigue, and hair loss. While these events are generally reversible and manageable, they can lead to serious outcomes or hospitalization. Cumulative toxicities of docetaxel include edema or other forms of fluid retention and neuropathy, which can limit tolerability to extended treatment cycles, and thus reduce the opportunity for durable disease control. Refer to the docetaxel prescribing information for further details regarding the anticipated risks and benefits of docetaxel.

Taken together, the safety data of MLN1117 and docetaxel as single agents indicate that the combination of these 2 agents may lead to increased gastrointestinal toxicities that should be generally reversible (see Section 6.9). The combination of MLN1117 and docetaxel may lead to exacerbation of non-overlapping toxicities and the occurrence of new toxicities that have not been identified with the single agents.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are:

Phase 1b

- To determine the DLTs, MTD, and RP2D of MLN1117 when administered PO in combination with docetaxel in patients with NSCLC

Phase 2

- To evaluate progression-free survival (PFS) as the primary efficacy measure of MLN1117 plus docetaxel versus docetaxel alone in patients with advanced NSCLC

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the safety and tolerability of MLN1117 plus docetaxel administered to patients with NSCLC **(Phase 1b and Phase 2)**
- To evaluate the PK of MLN1117 when administered with docetaxel **(Phase 1b and Phase 2)**
- To evaluate additional efficacy measures, such as response rate (RR), disease control rate, response duration, time to progression (TTP), and OS, of MLN1117 plus docetaxel versus docetaxel alone in patients with NSCLC **(Phase 2 only)**
- To evaluate PFS and additional efficacy measures of MLN1117 plus docetaxel versus docetaxel alone in different populations of patients with NSCLC, such as patients with squamous NSCLC versus nonsquamous NSCLC, and patients with squamous NSCLC with or without *PIK3CA* mutation and/or amplification (MUT/AMP) **(Phase 2 only)**

2.3 Exploratory Objectives

The exploratory objectives are:

- [redacted]
- [redacted]
- [redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints are:

Phase 1b

- DLTs, MTD, and RP2D

Phase 2

- PFS

3.2 Secondary Endpoints

The secondary endpoints are:

- Safety **(Phase 1b and Phase 2)**
  - Vital signs
  - Physical examination findings
  - 12-lead ECG
  - Clinical laboratory test results
  - AEs and SAEs
- Response rate (complete response [CR] + partial response [PR]), disease control rate (CR + PR + stable disease [SD]), duration of response (DOR), and TTP **(Phase 2 only)**
- OS **(Phase 2 only)**
- PK parameters for MLN1117 including, but not limited to, single-dose maximum (peak) concentration (C_{max}), T_{max}, AUC from zero to next dose (AUC_{τ}) and from time zero to last the time of the last quantifiable concentration (AUC_{last}), $t_{1/2}$, and apparent total body clearance (CL/F), as permitted by the data **(Phase 1b only)**
- MLN1117 plasma concentrations when administered 1 day after docetaxel **(Phase 2 only)**

3.3 Exploratory Endpoints

The exploratory endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is an open-label, phase 1b/adaptive phase 2 study of MLN1117 in combination with docetaxel versus docetaxel alone in adult patients with NSCLC.

This study consists of a Phase 1b dose escalation phase and an adaptive, randomized Phase 2 expansion phase. The patient population will consist of adults with locally advanced or metastatic NSCLC refractory or resistant to 1 prior line platinum-based, non-docetaxel-containing systemic chemotherapy (Phase 2). Patients who, after front-line, platinum-based, non-docetaxel-containing chemotherapy, have also been treated with 1 line of nivolumab or other immune-checkpoint inhibitors but progressed on or after that therapy, would also be eligible for Phase 2. Patients with NSCLC who have been treated with multiple prior lines of therapies are eligible for Phase 1b.

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. For each phase of the study, study drug will be administered in cycles of 21 days (see Section 6.1).

Docetaxel will be administered IV, and MLN1117 will be administered PO throughout the study.

The treatment duration for all patients in Phase 1b and Phase 2 may be up to 9 cycles of either docetaxel alone or docetaxel in combination with MLN1117. Patients receiving docetaxel plus MLN1117 may continue treatment with MLN1117 monotherapy beyond 9 cycles. Patients may continue to receive treatment until either disease progression (PD), occurrence of unacceptable toxicities, or death. The maximum duration of treatment will be 9 cycles (approximately 6 months) for patients receiving docetaxel alone or 12 months for patients receiving MLN1117 plus docetaxel (ie, 9 cycles of MLN1117 plus docetaxel followed by MLN1117 alone) unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued treatment beyond 9 cycles or12 months, respectively. Patients may discontinue study treatment at any time. Patients will attend the End-of-Treatment (EOT) visit 30 to 40 days after receiving their last dose of study drug.

Patients will continue to be followed after discontinuation of study treatment to collect OS data for a period of up to 12 months (after last dose of study treatment). In addition, for patients who discontinue treatment due to reasons other than PD, PFS data will be collected during the posttreatment follow-up period of up to 6 months after the last dose of study drug, and OS data collection will continue until death, withdrawal of consent for further follow-up, or 12 months following the last dose of study drug.

Throughout the study, AEs will be assessed, and laboratory values, vital signs, and ECGs will be obtained per the Schedules of Events to evaluate the safety and tolerability of MLN1117 alone or in combination with docetaxel. 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.[11] Dose-limiting toxicities are defined in Section 6.2.

Radiological tumor evaluations (computed tomography [CT] scan with IV contrast or magnetic resonance imaging [MRI] as clinically indicated of the chest, abdomen, and pelvis) will be used to evaluate disease response according to modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1).[12] Radiographic tumor evaluations and disease assessment will be performed by the investigator at the time points

specified in the Schedules of Events. In the Phase 2 portion of the study, a copy of all radiographic images with measurements will be sent to a central imaging vendor for the purpose of retrospective review by the sponsor; however, central radiologic evaluation is not planned for response assessment during the conduct of the study.

In addition to objective response assessment per modified RECIST guidelines, in Phase 2 of the study, [redacted] and treatment on physical, role, emotional, cognitive, and social functioning.

Blood samples for analysis of circulating tumor DNA will be collected at baseline in all patients. Subsequent samples will be obtained at the time points specified in the Schedules of Events and analyzed for the presence and clone frequency of somatic mutations frequently reported in solid tumors including *PIK3CA* mutations. Correlative studies will be performed to compare the mutation data generated from circulating tumor DNA with that from tumor tissue DNA. Dynamic changes in mutant clone frequency measured in circulating tumor DNA over the course of treatment will be evaluated in relation to objective response and disease status.

In addition, archived or fresh biopsy tumor tissue samples collected during screening will be analyzed for somatic alterations and other biomarkers that may relate to sensitivity or resistance to MLN1117 plus docetaxel.

Pharmacokinetic samples will be collected as specified in the Pharmacokinetic Sampling Schedules to characterize the PK of MLN1117.

4.1.1 Phase 1b (Dose Escalation)

Approximately 15 patients with NSCLC regardless of histology (squamous or nonsquamous) will be enrolled in this phase of the study. To determine the DLTs, MTD, and RP2D of MLN1117 plus docetaxel, a 3 + 3 dose escalation scheme (see Section 6.3) with a fixed dose of docetaxel and varying dose levels of MLN1117 will be used.

During a 21-day cycle of treatment, docetaxel (36 mg/m^2) IV will be administered on Days 1 and 8, and MLN1117 tablets (planned doses of 300, 600, and 900 mg) will be administered PO on a weekly schedule that includes 3 consecutive dosing days per week

(eg, Days 2, 3, 4, 9, 10, 11, 16, 17, and 18). If MTD or RP2D is not achieved by 900 mg, higher dose levels at 300 mg increments may be evaluated. More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators if such measures are needed for patient safety or for a better understanding of the dose–related toxicity or exposure of MLN1117 plus docetaxel.

If MLN1117 de-escalation is warranted, the daily dose of MLN1117 may be reduced or the number of treatment days per week may be reduced (eg, from 3 days to 2 days, or further to 1◦day); see Section 6.1 for details.

Testing of escalating MLN1117 doses in combination with a fixed docetaxel dose and schedule is planned. However, if frequent docetaxel dose modifications are necessary when administered in combination with MLN1117, the fixed dose of docetaxel may be decreased (eg, –1 dose level) based on discussion and agreement between investigators and the Millennium project clinician; see Section 6.1.

4.1.2 Phase 2 (Dose Expansion)

In Phase 2, the expansion phase of the study, up to 140 patients may be treated with the dose of MLN1117 that in combination with docetaxel is identified in Phase 1b as the RP2D (Arm A) or docetaxel alone (Arm B).

- Arm A: docetaxel 36 mg/m^2 IV on Days 1 and 8 of a 21-day cycle plus MLN1117 tablets, at the dose determined in Phase 1b, on Days 2, 3, 4, 9, 10, 11, 16, 17, and 18 of a 21-day cycle. (An alternative combination dosing regimen of MLN1117 plus docetaxel may be used based on the RP2D decision in Phase 1b if deemed appropriate by the sponsor.)

- Arm B: docetaxel 75 mg/m^2 IV once every 3 weeks (per approved prescribing information) with dosing on Day 1 of each 21-day cycle

Phase 2 of the study will use a sequential, multistage Bayesian adaptive design and will consist of up to 3 parts as described below. Each part is designed to evaluate MLN1117 plus docetaxel versus docetaxel alone in a distinct population of NSCLC. The study will start with Part 1 in patients with NSCLC inclusive of all histological types and all *PIK3CA* genotypes (*PIK3CA* mutation, amplification, or wild-type). The decision whether to proceed to Part 2 and expand the study to a specific histological type (either squamous or

nonsquamous) of NSCLC will be dependent on the efficacy data from Part 1. If patients with squamous NSCLC are selected for Part 2, the efficacy data from Part 2 will then be used to decide whether to proceed to Part 3, which will evaluate patients with a *PIK3CA* (MUT/AMP) squamous NSCLC. Each part of the adaptive Phase 2 portion of the study is designed as a stand-alone, randomized study evaluating PFS as the primary efficacy measure between the 2 treatment arms (MLN1117 plus docetaxel vs docetaxel alone). There will be a primary, event-driven analysis of PFS after each part of the adaptive Phase 2 portion of the study.

Phase 2 of the study may consist of 3 parts:

- Part 1: NSCLC (see Section 4.1.2.1)
- Part 2: Histology-specific NSCLC (see Section 4.1.2.2)
- Part 3: Histology- and genotype-specific NSCLC (see Section 4.1.2.3)

4.1.2.1 Phase 2, Part 1

Approximately 60 patients with NSCLC will be enrolled in this part of the study. On the basis of histology confirmed at screening, patients will be assigned to 1 of 2 cohorts:

- Cohort 1: up to 30 patients with squamous NSCLC
- Cohort 2: up to 30 patients with nonsquamous NSCLC

In each cohort, patients will be randomized 1:1 to treatment with MLN1117 plus docetaxel (Arm A) or docetaxel alone (Arm B).

The primary analysis of PFS will be performed when 50 events (death or PD) have been observed in 60 patients. On the basis of this analysis, the study may be stopped for efficacy or futility (See Section 8.1). If neither the efficacy nor the futility boundary is met, a subgroup analysis of PFS based on histology will be performed. A preferred histology (squamous or nonsquamous) will be determined, and the study will proceed to Part 2. If a preferred histology cannot be determined, 20 additional patients (10 per histology) may be enrolled in Part 1, and a second analysis of PFS will be repeated when 65 events have occurred in 80 patients with NSCLC (40 squamous and 40 nonsquamous). If neither efficacy nor a preferred histology is determined during the second interim analysis, the study will be stopped.

4.1.2.2 Phase 2, Part 2

On the basis of the results of the primary analysis of Part 1, only 1 histology subtype will be selected for study in Part 2. Enrollment for Part 2, therefore, will be 1 of the following:

EITHER

- Up to 30 patients with squamous NSCLC randomized 1:1 to treatment Arm A or Arm B. This will provide a maximum of 60 patients with squamous NSCLC (Part 1 and Part 2 combined). *PIK3CA* genotypes (*PIK3CA* MUT/AMP versus *PIK3CA* wild-type [WT]) will be used as 1 of the stratification factors during randomization. To ensure that patients with *PIK3CA* MUT/AMP and WT are evenly distributed between the 2 treatment arms, before enrolling patients in Part 2, the central testing laboratory results of *PIK3CA* genotypes will be available for all patients with squamous NSCLC who have completed Part 1. Additional patients enrolled in Part 2 must have known *PIK3CA* genotype status based on either local or central testing laboratory results during screening. For patients enrolled based on the local genotype data, central laboratory verification will be performed shortly after enrollment. Central laboratory data will be used as the default in case of a discrepancy, and adjustment in patient assignment may be needed.

OR

- Up to 30 patients with nonsquamous NSCLC randomized 1:1 to treatment Arm A or Arm B. This will provide a maximum of 60 patients with nonsquamous NSCLC (Part 1 and Part 2 combined). Patients with nonsquamous NSCLC with known mutations in *EGFR*, *ALK*, and *KRAS* are excluded.

An analysis of PFS for Part 2 (on squamous or nonsquamous patients, as applicable) will be performed when 50 events (death or PD) have been observed in 60 patients.

- If patients with nonsquamous NSCLC are selected for enrollment in Part 2, before the analysis of PFS for Part 2, a central laboratory *KRAS* mutation test will be performed during the study to confirm *KRAS* WT status and to ensure that 60 *KRAS* WT patients with nonsquamous NSCLC were enrolled in Phase 2 (Part 1 and Part 2 combined) of the study. Patients will be enrolled in the study on the basis of their local site's *KRAS* mutational data or unknown status. Additional patients with *KRAS* WT nonsquamous NSCLC may be enrolled in Part 2 if needed to replace any

patients who may have been enrolled with a *KRAS* mutation as confirmed by central laboratory testing of *KRAS* mutation. The primary analysis of PFS will then be conducted on the data from patients with *KRAS* WT nonsquamous NSCLC.

- If patients with squamous NSCLC are selected for enrollment in Part 2, before enrolling patients in Part 3, a primary analysis of PFS for Part 2 (includes Part 1 and Part 2 combined) patients with squamous NSCLC will be performed. On the basis of this analysis, the study may be stopped for either efficacy or futility (see Section 8.1), or up to 30 additional patients with *PIK3CA* MUT/AMP squamous NSCLC will be enrolled in Part 3.

4.1.2.3 Phase 2, Part 3

On the basis of the results of the primary analysis of Part 2 (for squamous only), up to 30 patients with *PIK3CA* MUT/AMP squamous NSCLC may be enrolled in Part 3 and randomized 1:1 to treatment Arm A or Arm B. This will provide a maximum of 60 patients (Parts 1, 2, and 3 combined) based on an estimated 50% incidence of *PIK3CA* mutations and amplification in squamous NSCLC.

Patients enrolled in Part 3 must have *PIK3CA* MUT/AMP per either local or central laboratory data available during screening. For patients enrolled based on the local genotype data, central laboratory verification will be performed shortly after enrollment. Central laboratory data will be used as the default in case of a discrepancy, and replacement of patients may be needed for those who may have been enrolled with wild-type *PIK3CA* as confirmed by a central laboratory. The primary analysis of PFS will be conducted when 50 events (PD or death) occur in 60 patients with *PIK3CA* MUT/AMP squamous NSCLC.

4.2 Number of Patients

Approximately 75 to 155 patients will be enrolled in this study from up to 35 study centers in North America and Europe. Enrollment is defined as the time of the initiation of the first dose of study drug.

4.3 Duration of Study

Treatment duration for all patients in Phase 1b and Phase 2 may be up to 9 cycles of either docetaxel alone or docetaxel in combination with MLN1117. Patients receiving docetaxel plus MLN1117 may continue treatment with MLN1117 monotherapy beyond 9 cycles. Patients may continue to receive treatment until either PD, occurrence of unacceptable

toxicities, or death. The maximum duration of treatment will be 9 cycles (approximately 6 months) for patients receiving docetaxel alone or 12 months for patients receiving MLN117 plus docetaxel (ie, 9 cycles of MLN1117 plus docetaxel followed by MLN1117 alone) unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued treatment beyond 9 cycles or 12 months, respectively. Patients may discontinue study treatment at any time. Patients will attend the EOT visit 30 to 40 days after receiving their last dose of study drug.

After EOT, patients will be followed for PFS and OS. For those patients who discontinue MLN1117 for any reason other than radiographic disease progression, CT (with contrast) or MRI scans should be completed every other cycle to further assess disease status until PD (per modified RECIST, Version 1.1)[12], start of an alternative therapy, or 6 months after the last dose of study drug. Patients who experience PD on or off study treatment will be contacted by phone every 3 months to assess for OS and for subsequent anticancer therapy. The OS follow-up period will be up to 12 months after the patient's last dose of study treatment. The final analyses for the clinical study report may be conducted after prespecified events (PD and death) have occurred for the event-driven PFS analysis conducted on the last Part of Phase 2 that has been completed (see Section 8.1).

The study will be terminated 6 months after the last patient completes an EOT study visit.

It is anticipated that this study will last for approximately 24 to 36 months on the basis of the sequential and adaptive design of Phase 2 of the study.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Male or female patients 18 years of age or older at time of consent.

2. Patients must have a histologically and/or cytologically confirmed diagnosis of NSCLC (squamous or nonsquamous). The following apply to Phase 2 of the study:

    - Squamous NSCLC:

- Patients with diagnosis of mixed squamous and nonsquamous (or adenosquamous) NSCLC are acceptable.

- Nonsquamous NSCLC:

  - Patients with known driver mutations (*EGFR* and *ALK*) indicated for front-line targeted therapy are excluded (local mutation data can be used for eligibility).

  - Patients with known *KRAS* gene mutations are excluded (local mutation data can be used for eligibility).

3. Patients must have locally advanced or metastatic disease (Stage IIIb or Stage IV) with radiographically or clinically evaluable lesions:

   - Measurable disease per modified RECIST criteria (Version 1.1)[12] by radiographic techniques (CT or MRI) is required for Phase 2 of the study only.

4. Patients must have experienced failure of at least 1 prior chemotherapy regimen:

   - For Phase 2 of the study:

     - Patients must have received 1 prior platinum-based chemotherapy regimen (excluding a docetaxel-containing regimen) for advanced or metastatic (Stage IIIb or Stage IV) disease followed by documented PD.

       - A drug provided as maintenance therapy following cytotoxic chemotherapy will be considered to be part of that regimen.

       - Patients who received prior therapy with paclitaxel as a part of the platinum-based doublet front-line regimen without PD on therapy are eligible for this trial.

       - Patients who, after the front-line, platinum-based, non-docetaxel-containing chemotherapy, have been treated with 1 line of nivolumab or other immune-checkpoint inhibitors but progressed on or after the therapy, are eligible.

- For Phase 1b of the study:
    - Patients who have experienced failure of multiple lines of prior chemotherapy are eligible.

5. The patient must have archived or fresh tumor biopsy samples obtained during screening sufficient for genotyping (Phase 2 only).
    - Enrollment in Phase 2 is contingent on the local or central laboratory confirming receipt of an adequate amount of tissue including sufficient DNA for analysis.
6. Patients must have adequate organ function, before the first dose of study drug, including the following:
    - Bone marrow reserve: absolute neutrophil count ≥ 1.5 × 109/L, platelet count ≥ 100 × 109/L, hemoglobin ≥ 9 g/dL
    - Hepatic: total bilirubin ≤ the upper limit of the normal range (ULN), transaminases (AST and ALT) ≤ 1.5 × ULN, alkaline phosphatase (ALP) ≤ 2.5 × ULN
    - Renal: serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance > 50 mL/min based either on Cockroft-Gault estimate (see Section 14.2) or based on a 12- or 24-hour urine collection
    - Metabolic: hemoglobin A1c (HbA1c) ≤ 6.5%; fasting serum glucose ≤ 130 mg/dL; fasting triglycerides ≤ 300 mg/dL
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (refer to Section 14.1).
8. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Section 14.5) at the same time, from the time of signing the informed consent through 30 days (or

longer, as mandated by local labeling [eg, USPI, SmPC, etc]) after the last dose of study drug, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of MLN1117 and, for docetaxel, for as long as is mandated by local labeling (eg, USPI, SmPC, etc); or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

10. Suitable venous access for the study-required blood sampling, including PK and PD sampling.

11. Recovered (ie, ≤ Grade 1 toxicity or eligibility per this protocol is met) from the reversible effects of prior anticancer therapy.

12. In the opinion of the investigator, the patient or legal guardian is capable of understanding and complying with protocol requirements for the duration of the study.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study or randomized to treatment.

1. Previous treatment with a PI3K or AKT inhibitor.

2. Prior cancer therapy or other investigational therapy within 2 weeks before the first administration of study drug or failed to recover from the reversible effects of prior anticancer therapies. For prior therapies with a half-life longer than 3 days, the interval must be at least 28 days before the first administration of study drug, and the patient must have documented PD.

3. Poorly controlled diabetes mellitus defined as HbA1c > 6.5% (see Inclusion Criterion 6); patients with a history of transient glucose intolerance due to corticosteroid administration are allowed.

4. The patient has taken strong inhibitors or strong inducers of CYP3A4 within 14 days before the first dose of study drug (see Section 14.3).

5. The patient has taken histamine-H_2 receptor antagonists and/or neutralizing antacids within 24 hours before the first administration of study drug.

6. The patient has taken proton pump inhibitors within 7days before the first administration of study drug.

7. The patient has a condition that requires the concomitant use of any of the excluded medications, supplements, or food products listed in Section 6.6 during the course of the study.

8. The patient has any clinically significant co-morbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease (specified below), active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study.

   Patients with any of the following cardiovascular conditions are excluded:

   - Acute myocardial infarction within 6 months before starting study drug

- Current or history of New York Heart Association Class III or IV heart failure (see Section 14.4)

- Evidence of current uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or ECG evidence of acute ischemia or active conduction system abnormalities

- Fridericia's corrected QT interval > 475 milliseconds (msec) (males) or > 450 msec (females) on a 12-lead ECG during the Screening period

- Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that in the opinion of the investigator are considered to be clinically significant

9. Known, previously diagnosed human immunodeficiency virus infection or active chronic hepatitis B or C. Specific screening for chronic viral illness is at the discretion of the site or local institutional review board (IRB).

10. The patient has brain metastasis, except for those patients who have completed definitive therapy, are not on steroids, have a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids, and do not have neurologic dysfunction that would confound the evaluation of neurologic and other AEs.

11. Patients with active secondary malignancy that requires treatment. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection and are considered disease-free at the time of study entry.

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

13. Male patients who intend to donate sperm during the course of this study or 120 days after receiving their last dose of study drug.

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

15. Unwilling or unable to abide by the requirements of this study.

16. The patient is an immediate family member, study site employee, or in a dependant relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling), or they may consent under duress.

6. STUDY DRUG

6.1 Study Drug Administration

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

Study drug will be administered in 21-day dosing cycles. Cycles are repeated every 3 weeks (21 days). In Phase 1b (dose escalation), a 3 + 3 dose escalation will be used (see Section 6.3). In this phase of the study, docetaxel (36 mg/m^2) IV will be administered on Days 1 and 8 of the 21-day cycle. MLN1117 tablets (planned doses of 300, 600, and 900 mg) will be administered PO once daily on Days 2, 3, 4, 9, 10, 11, 16, 17, and 18 of the 21-day cycle.

During Phase 1b, if MLN1117 de-escalation is warranted, the daily dose of MLN1117 may be reduced or the number of treatment days per week may be reduced (eg, from 3 days to 2 days, or further to 1◦day) while maintaining the same weekly MLN1117 total dose. Subsequent escalation may be permitted based on observed safety and tolerability data. These decisions will be made jointly by investigators and the Millennium project clinician. The alternative MLN1117 regimen may be carried forward into Phase 2 of the study if deemed appropriate by the sponsor, in consultation with the investigators.

Testing of escalating MLN1117 doses in combination with a fixed docetaxel dose and schedule is planned. However, if frequent docetaxel dose modifications are necessary when administered in combination with MLN1117, the fixed dose of docetaxel may be decreased (eg, –1 dose level) based on discussion and agreement between investigators and the Millennium project clinician. If decreased, the lower docetaxel dose may be carried forward into Phase 2 of the study if deemed appropriate by the sponsor, in consultation with the investigators.

In Phase 2 (dose expansion), Parts 1, 2, and 3, patients will be randomized to 1 of 2 treatment arms (Arm A or Arm B). Patients randomized to Arm A will receive docetaxel (36 mg/m^2) IV on Days 1 and 8 of the 21-day cycle. MLN1117 tablets, at the dose determined in Phase 1b, will be administered PO once daily on Days 2, 3, 4, 9, 10, 11, 16, 17, and 18 of the 21-day cycle. (An alternative MLN1117 or docetaxel dosing regimen may be used based on the RP2D decision in Phase 1b if deemed appropriate by the sponsor.) Patients randomized to Arm B will receive docetaxel (75 mg/m^2) on Day 1 of each 21-day cycle.

During each phase of the study, patients will be treated with a maximum of 9 cycles of either docetaxel alone or docetaxel plus MLN1117. Patients treated with docetaxel plus MLN1117 may receive subsequent MLN1117 monotherapy until PD, occurrence of unacceptable toxicities, or death. The maximum duration of treatment for patients will be 12 months unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued treatment beyond 12 months. Patients will continue to be followed after discontinuation of study drug to collect PFS and OS data. Patients may withdraw from therapy at any time.

6.1.1 MLN1117 Administration

MLN1117 will be administered PO on an empty stomach in the morning (ie, approximately 1 hour before a meal or 2 hours after a meal) with approximately 8 oz (240 mL) of water. Patients should be instructed to take their study medication at approximately the same time on each dosing day and to not take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. If a patient fails to take their MLN1117 dose within the time frame specified, the dose should be skipped and considered a missed dose. Patients should record any missed doses in their dosing diary (see the Study Manual) and resume dosing at the next scheduled time with the prescribed dosage. Additional information can be found in the Pharmacy Manual.

If severe emesis or mucositis prevents the patient from taking scheduled doses of MLN1117, that dose will be skipped. If emesis occurs after MLN1117 study medication ingestion, the dose will not be re-administered, and patients should resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diaries (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses.

6.1.2 Reference/Control Therapy: Docetaxel Administration

Please refer to the docetaxel prescribing information for further details regarding docetaxel administration.

6.1.2.1 Docetaxel Premedication

Premedication before and/or concomitant with docetaxel, including corticosteroids and anti-emetics, will be administered in accordance with the recommendations in the docetaxel prescribing information. Appropriate institutional practices consistent with docetaxel label and recommendation should be followed. All patients receiving docetaxel should be premedicated with corticosteroids to reduce the incidence and severity of fluid retention and hypersensitivity reaction. For example, dexamethasone 16 mg per day (eg, 8 mg BID) may be used for 3 days starting 1 day before docetaxel when docetaxel is administered every 3 weeks. Other premedications including, but not limited to, 5-hydroxytryptamine (5-HT3) anti-emetics may be administered per the local standard of care on the day of docetaxel administration.

6.1.2.2 Docetaxel Infusion

Docetaxel will be administered at 75 mg/m^2 once every 3 weeks or at 36 mg/m^2 once weekly, 2 weeks on, 1 week off (see Section 6.1), as an IV infusion per local practice.

6.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010.[11] These criteria are provided in the Study Manual. Dose-limiting toxicity will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with MLN1117 plus docetaxel:

- Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting more than 7 consecutive days.
- Grade 4 neutropenia of any duration accompanied by fever and/or systemic infection, where fever is defined as a temperature of ≥ 38.5°C.
- Grade 4 thrombocytopenia lasting more than 7 consecutive days.
- ≥ Grade 3 thrombocytopenia of any duration accompanied with clinically significant bleeding.

- A platelet count < 10,000/mm^3 at any time.
- Any other ≥ Grade 4 hematologic toxicity.
- Grade 3 or greater nonhematologic toxicity with the following exceptions:
    - Grade 3 arthralgia/myalgia.
    - Brief (< 1 week) Grade 3 fatigue.
    - ≥ Grade 3 nausea and/or emesis that can be controlled to ≤Grade 1 or baseline in 1 week with the use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.
    - ≥ Grade 3 diarrhea that can be controlled to ≤ Grade 1 or baseline in 1 week with optimal supportive therapy.
    - Grade 2 fasting hyperglycemia lasting ≤ 14 days with optimal treatment or Grade 3 fasting hyperglycemia lasting ≤ 24 hours with optimal treatment.
    - Grade 3 rash lasting ≤ 7 days with optimal treatment that includes topical steroid treatment, PO antihistamines, and pulse PO steroids, if necessary.
    - Any other Grade 3 nonhematologic toxicity that can be controlled to ≤ Grade 1 or baseline in 1 week with appropriate treatment. In this setting, a course of action will be determined jointly by the investigators and the sponsor.
- Inability to administer at least 75% of planned doses of MLN1117 and/or docetaxel within Cycle 1 due to study-drug related toxicity.
- Any clinically significant occurrence that the investigators and sponsor agree would place study subjects at undue safety risk.

Although DLTs may occur at any point during treatment, only DLTs occurring during Phase 1b, Cycle 1, of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels for an entire dose-level cohort. Patients in both Phase 1b and Phase 2 will be monitored through all cycles of therapy for treatment-related toxicities.

6.3 Phase 1b Dose Escalation Rules

The dose escalation phase of the study is designed to determine the DLT, MTD, and RP2D of MLN1117 when given in combination with docetaxel. Approximately 15 patients are planned; the exact number of patients to be enrolled will depend on the number of dose-level cohorts, toxicities observed, and the PK results of the initial dose levels.

The dose intervals will follow a 3 + 3 dose escalation with a fixed dose of docetaxel and varying dose levels of MLN1117 (see Section 6.1**)** starting with the treatment of 3 patients at a planned dose-level cohort:

1. If 0 of 3 patients experiences DLT, the dose level is considered safe, and dose escalation will continue.

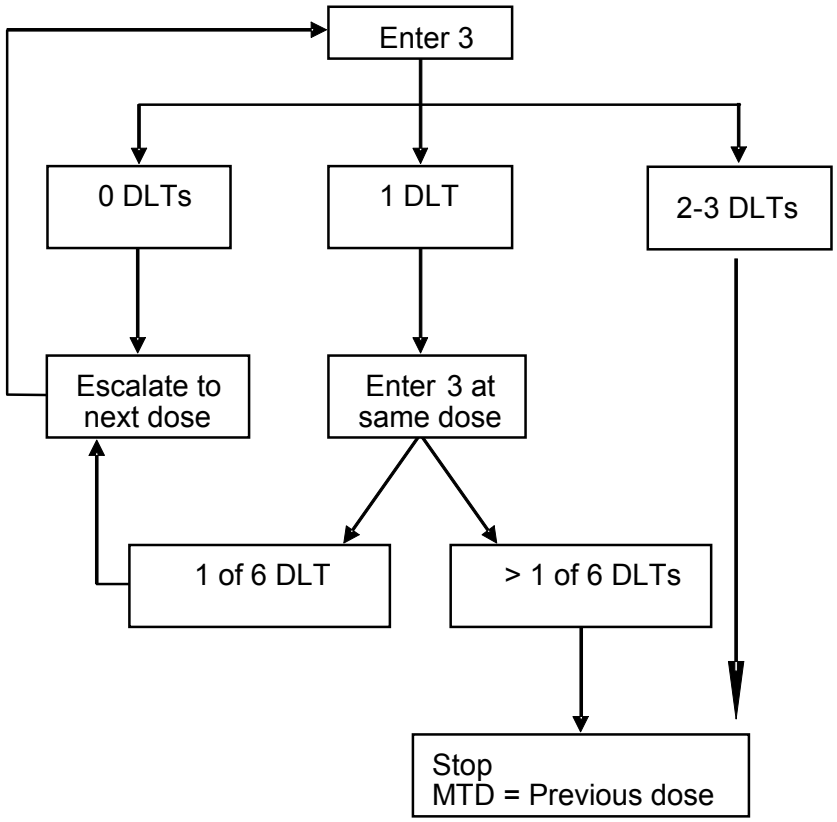
2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.

3. If 1 of 6 patients experiences DLT, the dose level is considered safe, and escalation will continue.

4. If 2 or more patients in any dose level experience DLT, the dose level is not considered safe, and escalation may not continue.

Figure 6.a is a diagrammatical representation of these rules.

Figure 6.a Dose Escalation Algorithm



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

Patients not receiving at least 75% of MLN1117 and/or docetaxel doses in Phase 1b, Cycle 1, for reasons other than DLTs will be replaced within the cohort.

If MTD or RP2D is not achieved by 900 mg, higher dose levels at 300 mg increments may be evaluated. More conservative dose escalation, evaluation of intermediate doses, expansion of an existing dose level, and evaluation of alternative regimens for both MLN1117 and docetaxel are all permissible, following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose–related toxicity or exposure of MLN1117 plus docetaxel. These alternative combination dosing regimen(s) may be carried forward into Phase 2 of the study if deemed appropriate by the sponsor, after consultation with the investigators.

6.4 Maximum Tolerated Dose and Recommended Phase 2 Dose

The MTD is defined as the highest dose level of MLN1117 when administered with weekly docetaxel at which no more than 1 of 6 patients experiences a DLT during the first cycle (21 days) of therapy in Phase 1b.

The RP2D of MLN1117 will be determined in Phase 1b on the basis of the totality of safety, tolerability, PK, and preliminary efficacy data (if available) observed in both Cycle 1 and Cycle 2 and beyond. The RP2D will not exceed the MTD.

While the primary escalation schema (see Figure 6.a) is designed to determine a classical Cycle 1-based MTD, dose escalation may be halted at any time after consultation between the sponsor and investigators if cumulative toxicity beyond Cycle 1 indicates that a given dose exceeds a tolerable RP2D.

6.5 Dose Modification Guidelines

Patients on study drug(s) in both Phase 1b (dose escalation) and Phase 2 (dose expansion) of the study will be evaluated weekly for Cycle 1 (Days 1, 2, 8, 9, and 16) and on Day 1 and Day 8 (docetaxel dosing days for the first 9 cycles) of every cycle between Cycles 2 and 9, and then on Day 1 of every cycle thereafter following discontinuation of docetaxel for possible toxicities that may have occurred after the previous dose(s).

Toxicities are to be assessed according to the NCI CTCAE, Version 4.03, effective date 14 June 2010.[11] The causal relationship of each AE should be assessed in relation to MLN1117 and in relation to docetaxel so that the dose modifications can be made accordingly. Administration and dose adjustment of docetaxel for patients treated with docetaxel alone or docetaxel in combination with MLN1117 will follow prescribing information for docetaxel and also the guidance on dose modification (Section 6.5.2.2) and management of clinical events (see Section 6.9). Minimal requirements per the docetaxel prescribing information have to be met before starting the next cycle or dose of docetaxel treatment (see Section 6.5.2.1). Dose modification guidelines for hematologic and nonhematologic toxicities are described below for both study drugs based on the type and severity of AEs, causality determination by investigators, and safety and tolerability profiles of each of the study drugs. Further clarification can be obtained in consultation with the Millennium project clinician (or designee).

Per dose modification guidelines, patients who have the study drug held because of treatment-related or possibly related AEs may resume study drug after resolution of the AE

but may either maintain the same dose level or have doses of study drug reduced (dose reduction) by at least 1 dose level. Docetaxel may be reduced from 75 mg/m^2 to 55 mg/m^2 or from 36 mg/m^2 to 30 mg/m^2 for the docetaxel alone and docetaxel plus MLN1117 arm, respectively. When a dose reduction of MLN1117 occurs, the MLN1117 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. During Phase 2, depending on the MTD/RP2D determined during Phase 1b, MLN1117 dose reduction will follow, in general, an increment of 300 mg, or an increment of 100 mg for doses ≤ 300 mg. If initial dose adjustment does not provide sufficient relief, the dose of MLN1117 can be further reduced if the treating physician considers that the patient is benefiting from study treatment and may benefit at a further reduced dose of MLN1117. Up to 2 dose level reductions of MLN1117 due to AEs are generally recommended. If more than 2 dose reductions of MLN1117 are needed to manage MLN1117-related AEs, discontinuation of treatment should be considered unless the treating physician considers that the patient may benefit from continued study treatment after resolution of AEs to < Grade 1 or baseline, and consults with the sponsor.

If 1 study drug is delayed because of toxicity attributed to its use, the other study drug is to be administered as scheduled.

Treatment with MLN1117 plus docetaxel will use a weekly schedule that includes 3 consecutive dosing days per week for MLN1117. For management of toxicity for individual patients, dose adjustment of MLN1117 normally includes a reduction in dose levels. However, a reduction in the number of treatment days per week (eg, reducing dosing days from 3 to 2 days or further to 1 day) at the same dose level could also be considered during dose escalation following discussions and agreement between investigators and the sponsor. Alternative regimen(s) for docetaxel administration may also be incorporated following discussions and agreement between investigators and the sponsor.

6.5.1 Phase 1b Intrapatient Dose Escalation

Once the RP2D is determined, all patients in Phase 1b actively receiving MLN1117 and docetaxel at a dose lower than the RP2D for a minimum of 2 cycles, in the absence of PD or unacceptable treatment-related toxicity per the investigator, may dose escalate to the RP2D at the investigator's discretion and with the sponsor's approval. Patients in whom an increase in the dose of MLN1117 is being considered must have treatment-related AEs resolved to ≤ Grade 1 or baseline or to a level that is acceptable to the investigators

(nonhematologic toxicity must be ≤ Grade 2, and hematologic toxicities must be less than the minimal requirement for starting a new cycle of treatment).

6.5.2 Phase 1b, Cycle 1, Intrapatient Dose Reduction

Intrapatient dose reductions of MLN1117 are not permitted during Phase 1b, Cycle 1, of therapy unless the patient experiences a DLT attributed to MLN1117. Dose-limiting toxicities are defined in Section 6.2. If a patient experiences a DLT during Phase 1b, Cycle 1, treatment should be held, and the event will be counted toward the assessment of MTD for the given cohort. Patients experiencing DLTs in Phase 1b, Cycle 1, may continue in the study upon resolution of the toxicity; however, the dose of MLN1117 (in combination with docetaxel) will be reduced by at least 1 dose level (or by up to 50% if the patient is receiving the first dose level). Patients who receive a reduced dose of MLN1117 during Cycle 1 for reasons other than DLTs will be replaced for DLT evaluation and dose escalation. Dose delay and dose reduction of docetaxel per docetaxel retreatment criteria (see Section 6.5.2.1) and dose modification guidelines is allowed in Cycle 1 during Phase 1b. Frequency of docetaxel dose delay and reduction will be taken into account in determining the RP2D for MLN1117 when administered with weekly docetaxel.

6.5.2.1 Criteria for Beginning or Delaying a Docetaxel Cycle/Dose

The patient must meet the following criteria before starting the next dose of docetaxel in both the docetaxel plus MLN1117 and the docetaxel alone treatment arms:

- ANC ≥ 1500/mm^3
- Platelet count ≥ 100,000/mm^3
- Total bilirubin < ULN, ALT/AST < 1.5 × ULN, ALP < 2.5 × ULN

For patients treated with docetaxel alone, 1 dose of 75 mg/m^2 docetaxel is given per 21-day cycle. If a patient fails to meet the docetaxel retreatment criteria, the next cycle of docetaxel dosing should be delayed for 1 week while supportive care is given based on the local standard practice or as specified in Section 6.9. The patient should be re-evaluated after 1 week to determine whether the criteria for docetaxel retreatment have been met. If the criteria have not been met, further delay of the next cycle of docetaxel and re-evaluation of docetaxel retreatment criteria will occur at weekly intervals until all retreatment criteria are satisfied. Dose modification guidelines will be followed to determine whether the dose of docetaxel will be maintained or reduced when docetaxel dosing is resumed.

For patients treated with docetaxel plus MLN1117, 2 doses of 36 mg/m^2 docetaxel will be given on Day 1 and Day 8 of 21-day cycles. If the patient fails to meet retreatment criteria for docetaxel before Day 1 dosing in a given cycle, the start of the cycle will be delayed. If the retreatment criteria are not met for the Day 8 dosing of docetaxel, the Day 8 dose will be delayed to Day 15 (provided that all retreatment criteria are met on Day 15), and the cycle will be expanded to a 28-day cycle. If further delay is needed, the second dose of docetaxel will be withheld, and docetaxel will be resumed in the next cycle.

Discontinuation of study should be considered if there is a delay of a new cycle (due to Day 1 docetaxel dosing delay for both docetaxel alone and MLN1117 plus docetaxel arm) or a delay of Day 8 docetaxel dosing (for MLN1117 plus docetaxel arm only) for ≥ 21 days (≥ 3 weeks) because of lack of adequate recovery of the toxicities, except in the case of investigator-determined clinical benefit and discussion with the Millennium project clinician. If the toxicities that result in failure of meeting the docetaxel retreatment criteria are determined to be related to docetaxel and not to MLN1117, patients should continue to receive MLN1117 according to the planned dose and regimen. If in the investigator's opinion, MLN1117 contributes to the toxicities (related or possibly related) that lead to not meeting docetaxel retreatment criteria, dose delay or modification of MLN1117 should be considered per the dose modification guidelines in Section 6.5.2.2.

6.5.2.2 Dose Modification for Hematologic and Nonhematologic Toxicity: MLN1117 and Docetaxel

A decision regarding which study drug requires dose modification will be dependent upon the toxicity, its onset, and time course. The causal relationship of any reported events (AEs or SAEs) should be assessed by the investigator in relation to MLN1117 and in relation to docetaxel. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines and the causal relationship to one or both study drugs. Guidelines for dose modifications for hematologic and nonhematologic toxicity are presented in Table 6.a and Table 6.b, respectively. After discussion between the investigator and the Millennium project clinician, alternative dose modifications may be recommended to maximize exposure of study treatment while protecting patient safety.

Table 6.a Guidelines for MLN1117 and Docetaxel Dose Modifications for Hematologic Toxicity

NCI CTCAE Grade	MLN1117 Dose Modification[a] (For Patients Receiving MLN1117 Plus Docetaxel)	Docetaxel Dose Modification (For Patients Receiving MLN1117 Plus Docetaxel and Docetaxel Alone)
Neutrophil Count (ANC) Decreased		
Grade 2 or 3 (ANC < 1500-500/mm^3; < 1.5-0.5 × $10e^9$/L)	No change. Continue MLN1117 at same dose and schedule.	Hold docetaxel until neutrophil count ≥ 1500/mm^3 then restart docetaxel at 75 mg/m^2 or 36 mg/m^2.
Grade 4 (< 500/mm^3; < 0.5 × $10e^9$/L)	Hold MLN1117 until ANC ≥ 1500/mm^3, restart MLN1117 at same dose and schedule.	Hold docetaxel until neutrophil count resolved to ≥ 1500/mm^3 then restart docetaxel. If resolved ≤ 7 days, maintain the same dose (75 or 36 mg/m^2). If resolved in > 7 days, reduce dose to 55 mg/m^2 or 30 mg/m^2.
Febrile neutropenia (ANC < 1000/mm^3 and fever defined as a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour) OR Neutropenia (ANC < 1000/mm^3) with systemic infection	Hold MLN1117 until ANC ≥ 1500/mm^3 and fever resolved, then restart MLN1117 at same dose and schedule.	Hold docetaxel until neutrophil count ≥ 1500/mm^3 and fever and infection resolved, then restart docetaxel at 55 or 30 mg/m^2.
Thrombocytopenia		
Grade 1or 2 (PLT 50,000-100,000/mm^3; < 50-100 × $10e^9$/L)	No change. Continue MLN1117 at same dose and schedule.	Hold docetaxel until PLT ≥ 100,000/mm^3, then restart docetaxel at 75 or 36 mg/m^2.
Grade 3 (PLT 25,000-50,000/mm^3; < 25-50 × $10e^9$/L)	Hold MLN1117 until PLT ≥ 100,000/mm^3 or baseline, restart MLN1117 at same dose and schedule.	Hold docetaxel until PLT ≥ 100,000/mm^3. If resolved ≤ 7 days, maintain the same dose of docetaxel. If resolved > 7 days, restart docetaxel at 55 or 30 mg/m^2.
Grade 4 (PLT < 25,000/mm^3; < 25 × $10e^9$/L)	Hold MLN1117 until PTL ≥ 100,000/mm^3 or baseline, restart MLN1117 at same dose and schedule.	Hold docetaxel until PLT ≥ 100,000/mm^3 or baseline, restart docetaxel at 55 or 30 mg/m^2.

Table 6.a Guidelines for MLN1117 and Docetaxel Dose Modifications for Hematologic Toxicity

NCI CTCAE Grade	MLN1117 Dose Modification[a] (For Patients Receiving MLN1117 Plus Docetaxel)	Docetaxel Dose Modification (For Patients Receiving MLN1117 Plus Docetaxel and Docetaxel Alone)
PLT < 10,000 cells/mm^3 or clinically significant bleeding	Consider permanently discontinuing MLN1117, except in the case where the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient is not discontinued, then the MLN1117 dose will be reduced to at least 1 dose level lower when PLT ≥ 100,000/mm^3 and/or clinically significant bleeding is completely resolved.	Consider permanently discontinuing docetaxel, except in the case where the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient is not discontinued, then the dose of docetaxel will be reduced to 55 or 30 mg/m^2 or lower per local standard practice and agreement between investigator and sponsor when PLT ≥ 100,000/mm^3 and/or clinically significant bleeding is completely resolved.

Abbreviations: ANC = absolute neutrophil count; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PLT = platelet count.

a Patients receiving docetaxel plus MLN1117 may continue treatment with MLN1117 alone beyond 9 cycles. Following completion of Cycle 9, follow action for MLN1117 dose modifications.

Table 6.b Guidelines for MLN1117 and Docetaxel Dose Modifications for Nonhematologic Toxicity

NCI CTCAE Grade	MLN1117 Dose Modification[a] (For Patients Receiving MLN1117 Plus Docetaxel)	Docetaxel Dose Modification (For Patients Receiving MLN1117 Plus Docetaxel and Docetaxel Alone)
Hepatotoxicity		
ALT and/or AST > 1.5 ULN to ≤ 5 × ULN (Grade 1 or 2)	• When ALP > 2.5 × ULN together with bilirubin < ULN, hold MLN1117 until both ALT and AST ≤ 1.5 × ULN. or • When ALP < 2.5 × ULN together with bilirubin < ULN, hold MLN1117 until both ALT and AST < 2.5 × ULN. Then resume MLN1117 at the same dose and schedule. Refer to Section 6.9 for guidelines on hepatic transaminase elevations.	• When ALP > 2.5 × ULN together with bilirubin < ULN, hold docetaxel until both ALT and AST ≤ 1.5 × ULN. or • When ALP < 2.5 × ULN together with bilirubin < ULN, hold docetaxel until both ALT and AST < 2.5 × ULN. Then resume docetaxel at the same dose and schedule. Refer to Section 6.9 for guidelines on hepatic transaminase elevations.

Table 6.b Guidelines for MLN1117 and Docetaxel Dose Modifications for Nonhematologic Toxicity

NCI CTCAE Grade	MLN1117 Dose Modification[a] (For Patients Receiving MLN1117 Plus Docetaxel)	Docetaxel Dose Modification (For Patients Receiving MLN1117 Plus Docetaxel and Docetaxel Alone)
ALT and/or AST > 5 ULN to ≤ 20 × ULN (Grade 3)	• When ALP > 2.5 × ULN together with bilirubin < ULN, hold MLN1117 until both ALT and AST ≤ 1.5 × ULN. or • When ALP < 2.5 × ULN together with bilirubin < ULN, hold MLN1117 until both ALT and AST < 2.5 × ULN. Then: • If resolved < 7 days, resume MLN1117 at the same dose and schedule. • If resolved > 7days, reduce MLN1117 by 1 dose level. • If recurred, reduce MLN1117 by 1 dose level.	• When ALP > 2.5 × ULN together with bilirubin < ULN, hold docetaxel until both ALT and AST ≤ 1.5 × ULN. or • When ALP < 2.5 × ULN together with bilirubin < ULN, hold docetaxel until both ALT and AST < 2.5 × ULN. Then resume docetaxel at the same dose and schedule.
ALT and/or AST > 20 ULN (Grade 4)	• When ALP > 2.5 × ULN together with bilirubin < ULN, hold MLN1117 until both ALT and AST ≤ 1.5 × ULN. or • When ALP < 2.5 × ULN together with bilirubin < ULN, hold MLN1117 until both ALT and AST < 2.5 × ULN. Then reduce MLN1117 by 1 dose level or consider permanently discontinuing MLN1117 if associated with symptoms or recurred with a severity of Grade 4.	• When ALP > 2.5 × ULN together with bilirubin < ULN, hold docetaxel until both ALT and AST ≤ 1.5 × ULN. or • When ALP < 2.5 × ULN together with bilirubin < ULN, hold docetaxel until both ALT and AST < 2.5 × ULN. Then resume docetaxel at the same dose and schedule
Hyperglycemia		
Grade 2 (Fasting glucose value > 160-250 mg/dL; fasting glucose value > 8.9-13.9 mmol/L)	Continue MLN1117 at same dose and schedule. Refer to Section 6.9 for guidelines on hyperglycemia management.	Continue docetaxel at same dose and schedule. Refer to Section 6.9 for guidelines on hyperglycemia management.

Table 6.b Guidelines for MLN1117 and Docetaxel Dose Modifications for Nonhematologic Toxicity

NCI CTCAE Grade	MLN1117 Dose Modification[a] (For Patients Receiving MLN1117 Plus Docetaxel)	Docetaxel Dose Modification (For Patients Receiving MLN1117 Plus Docetaxel and Docetaxel Alone)
Grade 3 (> 250-500 mg/dL; > 13.9-27.8 mmol/L; hospitalization indicated)	Hold MLN1117 until hyperglycemia improves to ≤ Grade 2. Refer to Section 6.9 for guidelines on hyperglycemia management. Optimize antihyperglycemic therapy and resume MLN1117 based on timing of recovery. • ≤ 1 week: resume MLN1117 at same dose and schedule. • > 1 but ≤ 2 weeks or recurrent with antihyperglycemic treatment: reduce MLN117 dose to the next lower dose level for all subsequent cycles. • > 2 weeks: stop MLN1117 and discontinue subject from study.	Continue docetaxel at same dose and schedule. Refer to Section 6.9 for guidelines on hyperglycemia management
Grade 4 (> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences)	Hold MLN1117 until hyperglycemia is resolved to ≤ Grade 2. Refer to Section 6.9 for guidelines on hyperglycemia management. • ≤ 1 week: reduce MLN117 dose to the next lower dose level for all subsequent cycles. • > 1 week: discontinue.	Hold docetaxel until hyperglycemia improves to ≤ Grade 2. Refer to Section 6.9 for guidelines on hyperglycemia management.
Other Nonhematologic Toxicities		
Peripheral neuropathy Grade 3	Maintain the same dose/regimen of MLN1117 if determined to be unrelated.	Permanently discontinue docetaxel.

Table 6.b Guidelines for MLN1117 and Docetaxel Dose Modifications for Nonhematologic Toxicity

NCI CTCAE Grade	MLN1117 Dose Modification[a] (For Patients Receiving MLN1117 Plus Docetaxel)	Docetaxel Dose Modification (For Patients Receiving MLN1117 Plus Docetaxel and Docetaxel Alone)
All other Grade 3 nonhematologic toxicities with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to ≤ Grade 1 or baseline within 1 week with optimal anti-emetics and antidiarrheals following SOC • Transient Grade 3 fatigue (lasting < 1 week) • Grade 3 rash lasting ≤ 7 days with optimal treatment • Any other Grade 3 nonhematologic toxicity that can be controlled to ≤ Grade 1 or baseline in 1 week with appropriate treatment in 7 days	Hold MLN117 if determined to be related to MLN1117 until resolution to ≤ Grade 1, baseline, or a level acceptable by the investigator (must be ≤ Grade 2): • If resolved in ≤ 7 days, then maintain dose level. • If resolved in > 7 days, then dose reduce by 1 dose level. • If recurred, then dose reduce by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as ≥ Grade 3 for more than 21 days despite temporary disruption of study drug.	Hold docetaxel if determined to be related to docetaxel until resolution to ≤ Grade 1, baseline, or a level acceptable by the investigator (must be ≤ Grade 2): • If resolved in ≤ 7 days, then maintain dose level. • If resolved in > 7 days, then dose reduce by 1 dose level. • If recurred, then dose reduce by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as ≥ Grade 3 for more than 21 days despite of temporary disruption of study drug.
All other Grade 4 nonhematologic toxicities	Consider permanently discontinuing MLN1117 based on causality determination except when the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient is not discontinued, MLN1117 dose will be reduced to at least 1 dose level lower when toxicity resolves to ≤ Grade 1, baseline, or a level acceptable by the investigator (must be ≤ Grade 2).	Consider permanently discontinuing docetaxel based on causality determination when the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient is not discontinued, MLN1117 dose will be reduced to at least 1 dose level lower when toxicity resolves to ≤ Grade 1, baseline, or a level acceptable by the investigator (must be ≤ Grade 2).

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SOC = standard of care; ULN = upper limit of the normal range.

a Patients receiving docetaxel plus MLN1117 may continue treatment with MLN1117 alone beyond 9 cycles. Following completion of Cycle 9, follow action for MLN1117 dose modification and delay.

6.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Use of other investigational medicinal products or devices.
- 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 upon discussion with the Millennium project clinician).
- Strong inhibitors/inducers of CYP3A4 (see Section 14.3).
- Proton pump inhibitors (eg, esomeprazole, lansoprazole, pantoprazole).

6.7 Permitted Concomitant Medications and Procedures

Restricted use of H_2-receptor antagonists or neutralizing antacids is permitted under the following conditions:

- Treatment with H_2-receptor antagonists is not permitted less than 24 hours before and within 6 hours after receiving a dose of MLN1117. Examples of H_2-receptor antagonist include ranitidine, famotidine, cimetidine, and nizatidine.
- Treatment with neutralizing antacids is not permitted less than 4 hours before and within 6 hours after receiving a dose of MLN1117.

Oral contraceptive pills or any other type of hormonal contraception is permitted.

Additional concomitant medications and procedures are permitted in the course of the study to prevent and/or actively manage AEs related or not related to the study drug(s) unless prohibited as specified in the protocol (see Section 6.9).

6.8 Precautions and Restrictions

It is not known what effects MLN1117 has on human pregnancy or development of the embryo or fetus. Docetaxel can cause fetal harm when administered to a pregnant woman, based on its mechanism of action and findings in animals.[13, 14] Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and

male patients should use highly effective methods of contraception (see list provided in Section 14.5) through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Section 14.5) at the same time, from the time of signing of the informed consent form through 30 days (or longer, as mandated by local labeling) after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Female patients must agree to not donate eggs (ova) during the course of this study or 30 days after receiving their last dose of MLN1117 and, for docetaxel, for as long as is mandated by local labeling.

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

- Practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of MLN1117 and, for docetaxel, for as long as is mandated by local labeling; or
- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients must agree to not donate sperm during the course of this study or 120 days after receiving their last dose of MLN1117 and, for docetaxel, for as long as is mandated by local labeling.

6.9 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, granulocyte colony stimulating factor (G-CSF), blood products (red blood cell [RBC] and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO) guidelines or local institutional practice. However, these agents should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation (Phase 1b).

Please refer to the most recent docetaxel prescribing information (eg, SmPC, USPI, etc) for specific details regarding the management of docetaxel-related clinical events such as hypersensitivity reactions, respiratory disorders, fluid retention, cystoid macular edema, peripheral neuropathy, etc.

Hematologic Effect (Neutropenia, Thrombocytopenia, and Anemia)

Blood counts and hemoglobin should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Administration of study drug(s) should be modified per dose modification guidance in the protocol when the hematological toxicity occurs. Myeloid growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor) may be used to treat severe and/or febrile neutropenia according to ASCO guidelines. Platelet transfusion is allowed to manage severe thrombocytopenia to prevent and minimize bleeding according to ASH/ASCO guidelines. In general, platelet transfusion should be given prophylactically to patients with platelet counts < 10,000/microL or to any patients with signs of overt bleeding, such as oral purpura. Packed RBC transfusion is permitted, as necessary, per local institutional practice. In general, RBC transfusion is recommended to all symptomatic patients with anemia or any asymptomatic patients with hemoglobin ≤ 7 to 8 g/dL with the purpose of maintaining the hemoglobin between 8 and 10 g/dL depending on the patients' age, symptoms, and comorbid conditions.

Hyperglycemia

Fasting serum glucose will be tested at the study site per the clinical visit schedule as outlined in the Schedules of Events. In addition, patients who experience hyperglycemia on trial will be given a glucometer to monitor their daily predose FBG at home (see Section 7.4.15). Patients will be instructed to notify the study staff immediately with any abnormal readings (ie, ≥ 140 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. When hyperglycemia is resolved (based on FSG levels at a clinical visit), it is at the investigator's discretion to discontinue or continue, either daily or at a reduced frequency, in-home FBG monitoring. If continued in-home glucose monitoring is chosen by the investigator to observe any further irregularities in the FBG level, patients will continue to notify the investigator of FBG levels ≥ 140 mg/dL. If blood glucose levels are not well controlled or if a patient requires either PO antihyperglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. If no further irregularities are observed, the in-home glucose monitoring may be discontinued if the investigator approves. Guidelines for management of hyperglycemia are presented in Table 6.c.

Table 6.c Management of Hyperglycemia

Grade	Description	Treatment	MLN0117 Dose Modification
1	Fasting blood glucose > ULN to ≤ 160 mg/dL	Continue close monitoring of blood glucose or initiate oral antihyperglycemic agent.	None
2	Fasting blood glucose > 160 to ≤ 250 mg/dL	Initiate oral antihyperglycemic agent and/or insulin if clinically indicated. Endocrinologist consult recommended.	None
≥ 3	Fasting blood glucose > 250 mg/dL	Initiate oral antihyperglycemic agent and/or insulin if clinically indicated. Endocrinologist consult recommended.	Hold drug until ≤ Grade 2. Resume MLN1117 based on timing of recovery: • ≤ 1 week: resume at same dose and schedule. • > 1 but ≤ 2 weeks or recurrence: reduce to the next lower dose level. • 2 weeks: stop MLN1117 and discontinue patient from the study.

Table 6.c Management of Hyperglycemia

Grade	Description	Treatment	MLN0117 Dose Modification
Prevention/Prophylaxis			
• Monitor fasting serum glucose levels during clinic visits. • Monitor home glucometer test results if applicable. • 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 ≥ 140 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.			

Abbreviations: FBG = fasting blood glucose; HbA1c = hemoglobin A1c; ULN = upper limit of the normal range.

If any FSG reading performed in the clinic indicates hyperglycemia (FSG > 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 PO 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.

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 (FSG > ULN to ≤ 160 mg/dL) or consider initiating treatment with a PO antihyperglycemic agent, such as metformin. All patients with ≥ Grade 2 hyperglycemia (fasting serum glucose > 160 mg/dL) must be treated aggressively with PO antihyperglycemic agents and/or insulin as clinically indicated while continuing on MLN1117 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 PO QD, and titrate up to a maximum of 1000 mg PO BID as needed. Concurrent addition to metformin of dipeptidyl peptidase-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution because of the higher risk of inducing hypoglycemia in patients. The dose of PO antihyperglycemic agents should be adjusted in patients with renal insufficiency.

Elevations in Hepatic Transaminases

Please see Section 1 and the IB regarding MLN1117 nonclinical and clinical hepatic safety.

Information regarding hepatic impairment in patients with NSCLC receiving docetaxel can be found in the docetaxel prescribing information. Per the docetaxel prescribing information, docetaxel should not be given if bilirubin is > ULN or if AST and/or ALT is > 1.5 × ULN concomitant with ALP > 2.5 × ULN. Liver function test (ALT and AST) elevations increase the risk of severe or life-threatening complications of docetaxel. Liver function test monitoring is planned per the Schedules of Events, and laboratory results are required before each dose of docetaxel. The LFT retreatment criteria must be met before the next planned dose of docetaxel is given to a patient. If LFT retreatment criteria for docetaxel are not met, both study drugs will be delayed until the LFT elevation is resolved. Dose adjustment, if needed, will follow the dose modification guideline (see Section 6.5.2.2) when the study drugs resume. If the study drug has been held for 3 weeks because of a lack of resolution of LFT elevations, then permanent discontinuation of study drugs should be considered.

Idiosyncratic severe hepatic injury can occur with many drugs. With severe hepatic injury, the liver has diminished capacity to excrete conjugated (or direct) bilirubin. Thus, in the absence of overt biliary tract disease, when ALT and/or AST is ≥ 3×ULN and when concomitant total bilirubin is ≥ 2 × ULN (> 35% direct bilirubin), significant liver injury may be present. When no other reason can be found to explain the combination of increased hepatic transaminases and serum bilirubin, this event should be considered to be drug-induced liver injury (defined as Hy's Law) and should be reported as an SAE. The study drug must be discontinued, and the patient must follow up with a hepatologist or specialist. Serial liver chemistries should be followed twice weekly until the event stabilizes or hepatic transaminases and bilirubin return to pretreatment values.

If the liver event does not meet SAE criteria, but symptoms of hepatic injury such as anorexia, fatigue, nausea, or abdominal pain occur in the presence of hepatic transaminase elevations > 3× ULN, dosing should be discontinued and immediate notification of/discussion with the study project clinician is required (within 24 hours) regarding the patient's clinical status and follow-up plans.

Nausea and/or Vomiting

This study will not initially employ prophylactic anti-emetics before the first dose of the study drug during dose escalation. However, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. Additionally, anti-emetics could be used prophylactically as clinically indicated following the occurrence of the first event of study drug-related or possibly related nausea and/or vomiting. It is recommended that PO anti-emetics such as ondansetron and/or prochlorperazine, be used as initial therapies. An optimal antiemetic regimen that is defined to employ both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules should be used to control nausea and/or vomiting, if needed.

If ≥ Grade 3 study drug-related nausea and/or vomiting cannot be controlled by optimal antiemetic therapy within 7 days (not resolved to Grade 1 or baseline), dose modification guidelines for the study drug(s) should be followed (see Section 6.5.2.2).

Diarrhea

Prophylactic antidiarrheals will not be used in this study before dosing of study drug. However, diarrhea should be managed according to local standard practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of study drug and during the study.

Fluid Retention

Patients should be premedicated with PO corticosteroids before each docetaxel administration in both the MLN1117 plus docetaxel and docetaxel alone arm to reduce the incidence and severity of fluid retention. Dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day before docetaxel administration is recommended, or local institutional practice is followed. When fluid retention occurs during docetaxel treatment, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg. Patients developing edema may be treated with standard measures, such as salt restriction and PO diuretic(s).

Hypersensitivity Reactions

Patients should be closely observed for hypersensitivity reactions, especially during the first and second infusion of docetaxel. Severe hypersensitivity reactions characterized by

generalized rash/erythema, hypotension and/or bronchospasm, or very rarely anaphylaxis, have been reported in patients treated with docetaxel. Hypertension reactions may occur within a few minutes following initiation of a docetaxel infusion. If minor reactions such as flushing or localized skin reaction occur, interruption of therapy is not required. However, severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy per local institutional practice. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel. All patients should be premedicated with a PO corticosteroid before the initiation of the docetaxel infusion (see Fluid Retention, above).

Respiratory Disorders

Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported in patients receiving docetaxel treatment, and may be associated with fatal outcome.[13]

If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of docetaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming docetaxel treatment must be carefully evaluated. Investigators are instructed to consult the most recent local prescribing information (eg, SmPC, USPI, etc) for complete details regarding the administration and management of docetaxel.

6.10 Blinding and Unblinding

This is an open-label study.

6.11 Description of Investigational Agents

MLN1117 will be supplied as tablets for PO administration and will be available in the following 2 dose strengths:

- MLN1117 100 mg tablets
- MLN1117 300 mg tablets

MLN1117 tablets have been developed as an immediate release tablet for PO administration. The drug product formulation consists of a mixture of drug substance, microcrystalline cellulose, low substituted hydroxypropyl cellulose, sodium croscarmellose, colloidal silicon

dioxide, and magnesium stearate.

Docetaxel is a commercially available drug administered IV.

6.12 Preparation, Reconstitution, and Dispensation

MLN1117 will be provided in 30-cc high-density polypropylene (HDPE) bottles with child-resistant caps and an induction seal. MLN1117 bottles are to be dispensed according to the site procedures and according to instruction and guidelines provided in the study Pharmacy Manual, including the requirement that tablets are stored in their original containers. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN1117 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN1117 tablets.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

6.13 Packaging and Labeling

MLN1117 will be handled at the investigative site as open-label material. MLN1117 tablets will be provided in 14-count, 30-cc HDPE bottles with child-resistant caps and an induction seal. For both dose strengths, each bottle contains 14 tablets and will have a label containing pertinent study information, country-specific requirements, and a caution statement.

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

6.14 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN1117 study drug should be stored in the original bottles and stored at room temperature from 15°C to 30°C (59°F-86°F). All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All MLN1117 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 subjects, 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 MLN1117 is an investigational agent, it should be handled with due care. Patients will receive instructions for home storage and administration of MLN1117. Patients will receive diary cards to record dosing compliance of MLN1117.

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

Please refer to the site Pharmacy Manual/Study Manual for additional instructions.

Docetaxel should be stored according to that label and the instructions provided in the manufacturer's most recent package insert or Summary of Product Characteristics.

7. STUDY CONDUCT

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

7.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and other vendors as necessary, such as the interactive voice/web response system (IXRS) provider and the contract research organization team, may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

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

7.3 Treatment Group Assignments

A centralized randomization procedure via IXRS will be used to for treatment assignment. Patients will be randomized strictly sequentially at a center as they become eligible for randomization and will be stratified as detailed in Section 8.1.2. If a patient discontinues from the study, the randomization code will not be reused, and the patient will not be allowed to re-enter the study.

7.4 Study Procedures

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

7.4.1 Informed Consent

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

7.4.2 Patient Demographics

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

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.9.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedules of Events. Some physical examinations will be symptom directed, as noted in the Schedules of Events. All standard-of-care examinations will include a neurological assessment.

7.4.5 Patient Height and Weight

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

7.4.6 Vital Signs

Vital signs will be measured at the times specified in the Schedules of Events. Vital sign measurements include measurements of diastolic and systolic blood pressure, heart rate, and temperature.

7.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and within 3 days before the first dose of study drug. The results from these tests must be available and negative before the first dose of study drug is administered. If Cycle 1 Day 1 serum pregnancy test results will not be available before dosing, a urine pregnancy test may be performed. Urine pregnancy tests will also be performed on Day 1 of every cycle thereafter.

7.4.8 Eastern Cooperative Oncology Group Scale for Performance Status

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

7.4.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the electronic case report form (eCRF) from first dose through 30 days after last dose of study drug. See Section 6.6 and Section 6.7 for a list of medications and therapies that are prohibited or allowed during the study.

7.4.10 Adverse Events

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

7.4.11 Enrollment

A patient is considered to be enrolled in the study when the first dose of study drug is administered.

Procedures for completing the enrollment information are described in the Study Manual.

7.4.12 Electrocardiogram

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

7.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed using a central laboratory. Local laboratories may be used as required for acute management of AEs. Handling and shipment of clinical laboratory samples will be outlined in the study manual. Clinical laboratory evaluations will be performed as outlined below:

Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedules of Events. Hematology and serum chemistry laboratory results must be available and reviewed by the investigator before enrollment and study drug administration.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Glucose[a]
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium

a See the Schedules of Events for serum glucose samples that must be obtained while the patient is fasting (nothing except water) for 8 hours before the measurement.

Urinalysis

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

Metabolic Panel

Fasting Lipid Profile

- Cholesterol
- Triglycerides
- High-density lipoprotein (HDL) cholesterol
- Low-density lipoprotein (LDL) cholesterol

Other

- Hemoglobin A1c
- Creatinine clearance (calculated using the Cockroft-Gault estimate [see Section 14.2] or based on a 12- or 24-hour urine collection)

7.4.14 Fasting Serum Glucose

Fasting serum glucose will be measured at the time points specified in the Schedules of Events before administration of study drug. 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.

7.4.15 In-Home Daily Glucose Monitoring

Patients who experience hyperglycemia while on study will be given a glucometer to monitor their daily predose FBG at home. Patients will be instructed to fast overnight (nothing except water and medications after midnight or for a minimum of 8 hours) for each of these measurements.

Patients will be instructed to notify the study staff immediately of any abnormal readings (ie, ≥ 140 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. When hyperglycemia is resolved (based on FSG levels at a clinical visit), it is at the investigator's discretion to discontinue or continue, either daily or at a reduced frequency, in-home FBG monitoring. If continued in-home glucose monitoring is chosen by

the investigator to observe any further irregularities in the FBG level, patients will continue to notify the investigator of FBG levels ≥ 140 mg/dL. If blood glucose levels are not well controlled or if a patient requires either PO antihyperglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. If no further irregularities are observed, the in-home glucose monitoring may be discontinued if the investigator approves.

On study visit days where FSG is assessed in the clinic, the in-home daily fasting glucose monitoring does not need to be completed.

7.4.16 Disease Assessment

Patients will undergo CT scan with contrast as appropriate, MRI, x-ray, and/or bone scanning to monitor and assess disease progression, using modified RECIST criteria (Version 1.1).[12] Contrast CT scans of the chest, abdomen, and pelvis will be obtained at screening. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation using an imaging modality consistent with that used at screening. Objective assessments will be performed at each time point as described in the Schedules of Events. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents. In addition, during the Phase 2 portion of the study, a copy of the image(s) will be sent to a central imaging vendor for storage. Subsequent analysis of these images may be conducted at the sponsor's discretion. However, the response assessment during the study will be based solely on investigator assessment.

7.4.17 Archival Tumor Tissue and Tumor Biopsies

During the Phase 1b dose escalation phase, in the absence of archival tissue material, a fresh tumor specimen will be collected at screening only when a biopsy is performed per standard of care. Tissue samples (archival or fresh) are mandatory for all patients at screening in the Phase 2 dose expansion portion. Tumor tissue (either fresh or archival) samples will be analyzed for *KRAS* mutations and *PIK3CA* mutations and/or amplification (squamous patients only). In addition, the sample will be used for analysis of predictive biomarkers of MLN1117 in combination with docetaxel response including, but not limited to, somatic mutations.

Patients undergoing tumor biopsy procedures must have a platelet count > 75,000/mm^3 and activated partial thromboplastin time and prothrombin time/international normalized ratio within the normal range; must have an ECOG Performance Status of 0 or 1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. The tumor biopsy procedure will be performed per local standard care, for example, by core needle, under radiological guidance if indicated, or surgically with punch biopsy if the site of disease is superficial and palpable or visible. It is at investigator's discretion to determine a patient's eligibility for biopsy and decide with the patient's consent whether to perform a biopsy procedure based on a risk assessment to the patient.

The correlation of a panel of somatic mutations with MLN1117 activity in screening tumor biopsy samples and/or archival paraffin tumor tissue will be evaluated.

7.4.18 Pharmacokinetic Measurements

Blood samples will be collected for the determination of the plasma concentrations of MLN1117. Plasma PK samples will be collected at the time points specified in the Pharmacokinetic Sampling Schedules. The actual date and time of each PK sample collection and the date and time of MLN1117 dosing for the last most recent dose should be recorded accurately in the eCRF. Instructions for collecting and processing PK blood specimens are provided in the Study Manual.

7.4.19 DNA Measurements

[redacted]

[redacted]

In addition, the sample may be used for identification of gene polymorphisms related to study drug-related toxicity and/or clinical response. Detailed instructions for the collection, processing, and shipment of samples are provided in the Laboratory Manual.

Such analyses will be used to determine eligibility in Phase 2 Part 2 and Phase 2 Part 3.

7.4.20 [redacted]

[redacted] will be administered as specified in the Schedules of Events for the Phase 2 portion of the study only.

[redacted]

[redacted] will be collected as specified in the Schedules of Events, and they must be completed before other assessments are performed or study drug is administered.

7.5 Completion of Treatment

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

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

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

- AE
- Protocol violation
- PD
- Symptomatic deterioration
- Unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

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

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

Patients not receiving at least 75% of MLN1117 and/or docetaxel doses in Phase 1b, Cycle 1, for reasons other than DLTs will be replaced within the cohort.

7.8 Withdrawal of Patients From Study

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

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

- Other

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

7.9 Study Compliance

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

Patients will receive a sufficient quantity of ML1117 (unless in Arm B of Phase 2) for each treatment cycle and a diary in which to record their dosing. The study center staff will check the patient's diary versus the patient's supply of remaining MLN1117 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 (Progression-Free Survival and Overall Survival)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 2 months from last dose of study drug until PD for a maximum of 6 months from the date of the last dose of study drug. After the occurrence of PD, patients will continue to have OS follow-up visits. The OS information will be collected every 3 months until 12 months from the date of the last dose of study drug.

Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieval from online or other databases (eg, social security indexes). In addition, the start of another anticancer therapy will be collected.

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

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

Details for the statistical analysis will be provided in the statistical analysis plan (SAP). The SAP will be written by Takeda and will be finalized before database lock for the final analysis.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

8.1.1 Determination of Sample Size

Phase 1b

The number of patients enrolled in this study will be driven initially by the dose escalation part and by the dose expansion part. In Phase 1b (dose escalation), approximately 15 patients with NSCLC regardless of histology (squamous or nonsquamous) may be enrolled based on the dose escalation scheme outlined in Section 6.3.

Phase 2

Phase 2 of this study (dose expansion) will use a sequential, multistage, Bayesian adaptive design (see Figure 8.a) to allow either to favor all NSCLC patients or to select a subpopulation defined by histology characteristics or tumor DNA genotype. The primary efficacy endpoint is PFS (time from randomization to PD or death). Assuming an exponential distribution for PFS, 50 to 65 PFS events out of 60 to 80 patients with NSCLC; 50 PFS events out of 60 patients with squamous or nonsquamous NSCLC (Parts 1 and 2 combined); and 50 PFS events out of 60 patients with *PIK3CA* MUT/AMP squamous NSCLC (Parts 1, 2, and 3 combined), if applicable, will be required to target median PFS improvement of 2.5 months (median PFS of 2.5 months of single-agent docetaxel vs 5 months of MLN1117 plus docetaxel, HR = 0.5) in any of these populations with 80% power at the type I error of 0.05 (equal to HR $\leq$ 0.63 with 72% power based on the calculated posterior probability of success, see decision rules below for each part of

Phase 2). A maximum number of 140 patients will be randomized in a 1:1 ratio to receive either MLN1117 plus docetaxel or single-agent docetaxel, assuming an enrollment rate of 6 patients per month and a dropout rate of approximately 10%. The maximum of 140 patients included 80 patients with NSCLC, 60 patients with squamous or nonsquamous NSCLC (Parts 1 and 2 combined), and 60 patients with *PIK3CA* MUT/AMP squamous NSCLC (Parts 1, 2, and 3 combined).

Phase 2, Part 1

Approximately 60 patients with NSCLC will be enrolled in this part of the study. On the basis of histology confirmed at screening, patients will be assigned to 1 of 2 cohorts:

- Cohort 1: up to 30 patients with squamous NSCLC
- Cohort 2: up to 30 patients with nonsquamous NSCLC

In each cohort, patients will be randomized 1:1 to treatment with MLN1117 plus docetaxel or docetaxel alone. Before enrolling patients in Part 2, the primary analysis of PFS will be performed when 50 events are observed. On the basis of this analysis, the actual number of patients enrolled in Part 2 will be determined. The decision rules are:

1. If the posterior probability of overall hazard ratio ($HR_{overall}$) ≤ 0.63 is at least 72%, the study will stop for efficacy. MLN1117 plus docetaxel is considered as improving PFS over single-agent docetaxel in NSCLC patients.
2. If the posterior probability of $HR_{overall} \leq 0.63$ is less than 15%, the study will be terminated for futility.
3. If criteria 1 or 2 are not met, an adaptation rule will be employed to either define a subpopulation based on histology (squamous or nonsquamous) or decide whether to enroll additional patients with NSCLC (including both squamous and nonsquamous). The study will change to evaluate whether the PFS benefit of MLN1117 plus docetaxel over single-agent docetaxel in patients with squamous NSCLC is superior to that in patients with nonsquamous NSCLC or vice versa:

    3.1 If the posterior probability of squamous hazard ratio ($HR_{squamous}$) < nonsquamous hazard ratio ($HR_{nonsquamous}$) (larger treatment effect in squamous vs nonsquamous) is at least 60%, proceed to Part 2 to enroll additional 30 patients with squamous NSCLC.

3.2 If the posterior probability of $HR_{squamous} > HR_{nonsquamous}$ (smaller treatment effect in squamous vs nonsquamous) is at least 60%, proceed to Part 2 to enroll additional 30 patients with nonsquamous NSCLC.

If neither criterion 3.1 nor 3.2 is satisfied, 20 additional patients with NSCLC (10 squamous and 10 nonsquamous) will be randomized 1:1 to treatment with MLN1117 plus docetaxol or docetaxol alone. When 65 events out of the 80 patients with NSCLC (40 squamous and 40 nonsquamous) are observed, evaluation of criteria 1 and 2 will be performed. If neither criterion 3.1 nor 3.2 is met, the study will be terminated.

Phase 2, Part 2 (Histology Specific)

On the basis of the results of the primary analysis of Part 1, only 1 histology subtype will be selected for study in Part 2. Enrollment for Part 2, therefore, will be 1 of the following:

EITHER

- A maximum of 30 patients with squamous NSCLC (to provide 60 patients in Part 1 and Part 2 combined) will be randomized 1:1 to treatment with MLN1117 plus docetaxel or docetaxel alone stratified by prior therapy or *PIK3CA* mutational status. To ensure that patients with and without *PIK3CA* MUT/AMP are evenly distributed between the 2 treatment arms, before enrolling patients in Part 2, the local or central testing lab will confirm the histology and tumor DNA genotype of the patients who have completed Part 1. Additional patients enrolled in Part 2 must have histology and tumor DNA genotyping confirmed at screening.

OR

- A maximum of 30 patients with nonsquamous NSCLC (to provide 60 patients in Part 1 and Part 2 combined) will be randomized 1:1 to treatment with MLN1117 plus docetaxel or docetaxel alone.

When 50 events out of 60 patients are observed and the status of each patient's histology is available (squamous or nonsquamous), a primary analysis of PFS for Part 2 will be performed. If the nonsquamous subtype is selected for Part 2, the study will be terminated after Part 2. If the squamous subtype is selected, the study might further evaluate whether to proceed to Part 3.

- If patients with nonsquamous NSCLC are selected for enrollment in Part 2, before the analysis of PFS for Part 2, a central laboratory *KRAS* mutation test will be performed during the study to confirm *KRAS* WT status and to ensure that 60 patients with *KRAS* WT nonsquamous NSCLC were enrolled in Phase 2 (Part 1 and Part 2 combined) of the study. Patients will be enrolled in the study on the basis of their local site's *KRAS* mutational status. Additional patients with *KRAS* WT nonsquamous NSCLC may be enrolled in Part 2 if needed to replace any patients who may have been enrolled with a *KRAS* mutation as confirmed by central laboratory testing of *KRAS* mutation. The primary analysis of PFS will be conducted to evaluate whether MLN1117 plus docetaxel improves PFS in patients with nonsquamous NSCLC relative to single-agent docetaxel. If the posterior probability of $HR_{nonsquamous} \leq 0.63$ is at least 72%, MLN1117 plus docetaxel is considered as improving PFS over single-agent docetaxel in patients with nonsquamous NSCLC.

- If patients with squamous NSCLC are selected for enrollment in Part 2, before enrolling patients in Part 3, a primary analysis of PFS in patients with squamous NSCLC (Part 1 and Part 2 combined) will be performed.

  The decision rules are as follows:

  1. If the posterior probability of $HR_{squamous} \leq 0.63$ is at least 72%, the study will stop for efficacy. MLN1117 plus docetaxel is considered as improving PFS over single-agent docetaxel in patients with squamous NSCLC.

  2. If the posterior probability of $HR_{squamous} \leq 0.63$ is less than 15%, the study will be terminated for futility.

  3. If neither criterion 1 nor 2 is satisfied, the study will proceed to Part 3 to evaluate patients with *PIK3CA* MUT/AMP squamous NSCLC by enrolling an additional 30 patients with *PIK3CA* MUT/AMP squamous NSCLC.

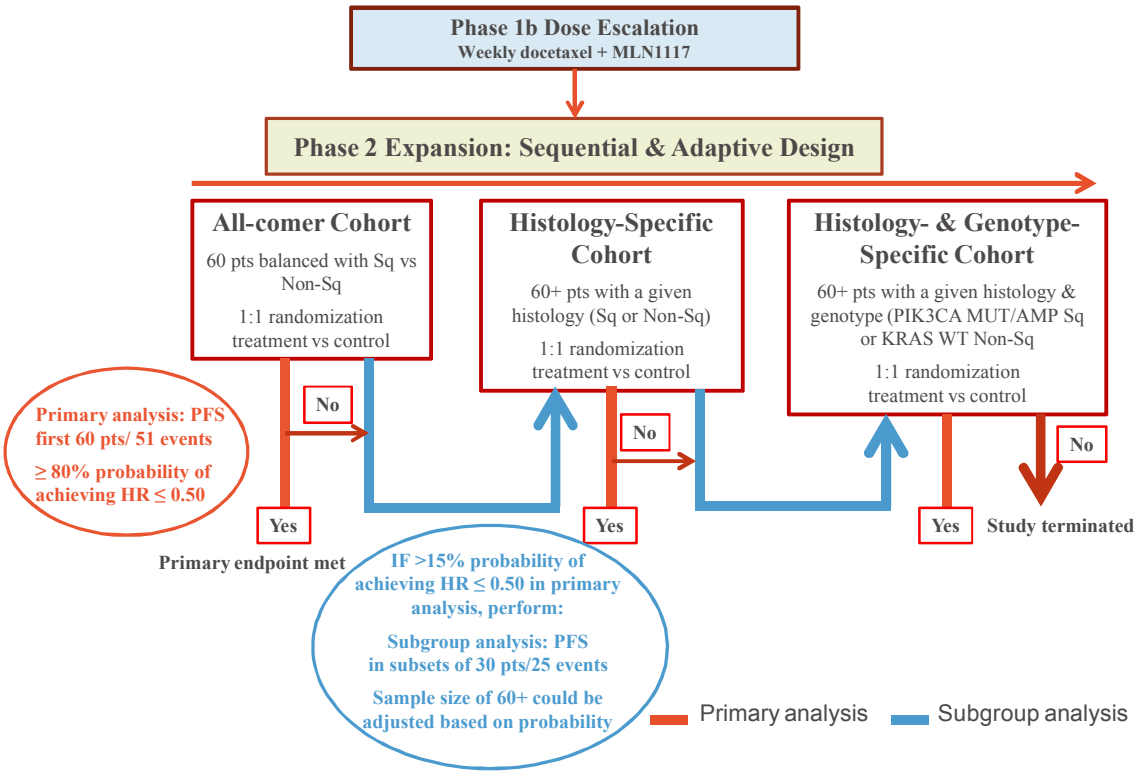
Phase 2, Part 3 (Histology and Genotype Specific)

Patients enrolled in Part 3 must have histology and tumor DNA genotyping confirmed at screening. On the basis of results of the primary analysis of Part 2, a maximum of 60 patients with *PIK3CA* MUT/AMP squamous NSCLC (Parts 1, 2, and 3 combined) will be enrolled in Part 3 and randomized 1:1 to treatment MLN1117 plus docetaxel or docetaxel alone. When 50 events out of 60 patients are observed, a primary analysis of PFS for Part 3

PIK3CA MUT/AMP squamous NSCLC (Parts 1, 2, and 3 combined) will be performed. If the posterior probability of squamous *PIK3CA* mutation and/or amplification hazard ratio ($HR_{MUT/AMP}$) ≤ 0.63 is at least 72%, MLN1117 plus docetaxel is considered as improving PFS over single-agent docetaxel in patients with *PIK3CA* MUT/AMP squamous NSCLC.

There may be 3 to 4 planned analyses (See Section 8.1.11).

Figure 8.a Phase 2, Sequential and Bayesian Design



Abbreviations: HR = hazard ratio; MUT/AMP = mutation and/or amplification; Non-Sq = nonsquamous; NSCLC = non-small cell lung cancer; PFS = progression-free survival; Sq = squamous; pts = patients.

8.1.2 Randomization and Stratification

In Phase 1b of the study, there is no randomization or stratification; all patients will receive MLN1117 plus docetaxel.

The randomization scheme for Phase 2 of the study will be generated by an independent statistician at Takeda who is not on the study team. Before dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an IXRS. Eligible patients will be randomized in a 1:1 ratio into either MLN1117 plus docetaxel or docetaxel alone, stratified by 1) 1 versus >1 prior therapies; or 2) *PIK3CA*

mutational status (*PIK3CA* MUT/AMP or *PIK3CA* WT). Enrollment to this study will be based on histology status (squamous or nonsquamous). The study will balance enrollment of patients with squamous and nonsquamous NSCLC (approximately 30 squamous and 30 nonsquamous). Genotyping will be conducted while the study is ongoing.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- **Safety population:** The Safety population is defined as all patients who receive at least 1 dose of MLN1117 plus docetaxel or 1 dose of docetaxel alone. Patients will be analyzed according to the treatment actually received. That is, those patients who are randomized to the MLN1117 plus docetaxel arm but received 1 dose of docetaxel will be included in the docetaxel arm, and those patients who are randomized to the docetaxel arm but received MLN1117 plus docetaxel will be included in the MLN1117 plus docetaxel arm for safety analyses.

- **Intent-to-Treat (ITT) population:** The ITT population is defined as all patients who are randomized and received at least 1 dose of any study drug. The ITT population will be used for the analysis of PFS, TTP, and OS. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

- **Response-Evaluable population:** The Response-Evaluable population is defined as all patients with NSCLC having measurable disease at baseline, who receive at least 1 dose of MLN1117 plus docetaxel or docetaxel alone, and have at least 1 postbaseline response assessment. The Response-Evaluable population will be used for the analysis of RR (CR +PR), disease control rate (CR + PR + SD), and DOR.

- **DLT-Evaluable population:** The DLT-Evaluable population, defined as all patients in the Phase 1b portion of the study who either experience DLT during Cycle 1 or complete treatment with at least 75% of the planned doses of MLN1117 plus docetaxel, and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred, will be used for analysis of DLT.

- **PK-Evaluable population:** The population of patients evaluable for the determination of the PK of MLN1117 is defined as all patients in the Phase 1 portion

of the study for whom there are sufficient dosing and MLN1117 concentration-time data to permit noncompartmental PK analysis.

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, unless specified otherwise. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, gender, race, weight, baseline disease characteristics, histology, and genotype status.

8.1.6 Efficacy Analysis

8.1.6.1 Analyses of Primary Efficacy Endpoints

Phase 1b

There is no primary efficacy endpoint in the Phase 1 portion of the study.

Phase 2

Primary Efficacy

The primary endpoint for the Phase 2 portion is PFS. Progression-free survival is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. The censoring method will be described in the SAP. Progression-free survival will be tested at the final analysis based on the ITT population. A 1-sided unstratified log-rank test will be used to compare the treatment arms with respect to PFS. In addition, an unadjusted Cox regression model will be used to estimate the hazard ratio and its 95% CI for the treatment effect. The Kaplan-Meier survival curves, 25^{th}, 50^{th} (median), and 75^{th} percentiles (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment arm.

8.1.6.2 Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints in the Phase 2 portion of the study include RR (CR + PR), disease control rate (CR + PR + SD), DOR, TTP, and OS. The estimate of the RR and

disease control rate (CR + PR + SD) will be presented with 2-sided 95% exact binomial CIs for each treatment arm. The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, Version 1.1. Fisher's exact tests will be performed for the comparison of RR and disease control rate between the treatment arms. Response rate (RR) and disease control rate will be analyzed based on the Response-Evaluable population.

Duration of response is defined as the time from the date of first documentation of a response to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

Time to progression is defined as the time from the date of randomization to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

Overall survival is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

Duration of response, TTP, and OS will be analyzed using the Kaplan-Meier method. Unstratified long-rank tests will be performed for the comparisons between the 2 treatment arms. Duration of response will be analyzed based on the responders in the Response-Evaluable population. Time to progression and OS will be analyzed based on the ITT population.

8.1.7 Exploratory Analysis

[redacted]

8.1.8 [redacted]

[redacted]

8.1.8.1 [redacted]

[redacted]

[redacted]

Particularly, the symptom (cough, dyspnoea, pain) improvement rate and time to symptom (cough, dyspnoea, pain) deterioration will be compared between treatment groups. Symptom improvement will be defined as a ≥ 10-point decrease from baseline, and symptom deterioration will be defined as a ≥ 10-point increase from baseline.

[redacted] will be used for scoring and handling missing data. Further investigation of missing patterns and details of imputation, including subsequent sensitivity analysis, may be considered.

8.1.9 Pharmacokinetics/Biomarkers

Pharmacokinetic Analysis

Individual and mean plasma concentrations will be plotted over time for MLN1117 (Cycle 1, Day 2). Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters, including, but not limited to, C_{max}, AUC_{last}, AUC_{inf}, and $t_{½}$ for MLN1117 (Cycle 1, Day 2), as permitted by the data. Descriptive statistics will be presented for plasma PK parameters of MLN1117 on Cycle 1 Day 2.

Pharmacokinetic data collected during the Phase 2 portion of the study (sparse PK) will be used only for future population PK analysis and may be combined with similar data from other studies of MLN1117, the results of which will not be presented in the clinical study report for this study. These concentration-time data in individual patients will, however, be listed.

Biomarkers

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

Pharmacogenomic Analysis

Genotyping of polymorphisms in genes encoding proteins involved in metabolism or disposition of MLN1117 may be performed, guided by emerging understanding of PK and clearance mechanisms of MLN1117. In addition, gene polymorphisms related to AEs and/or clinical response may be included in analysis. Individual germline genotype will be listed for each of the polymorphisms evaluated. Descriptive and graphical methods may be used to explore the relationship between genotype and selected PK parameters for those related to the metabolism or disposition of MLN1117. Polymorphisms identified for AEs and/or clinical response will be tabulated based on AE and/or clinical response criteria. Pharmacogenomic data from this study may be combined with similar data from other MLN1117 clinical studies evaluating genetic polymorphism effects on MLN1117 PK (eg, as a part of a future population PK analysis), the results of which will be presented in a separate report and will not be presented in the clinical study report for this study.

8.1.10 Safety Analysis

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

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

Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities 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 (ie, those events reported by ≥ 10% of all patients)

- SAEs

A listing of TEAEs resulting in study drug discontinuation will be provided.

Clinical laboratory parameters will be summarized across time on study. Shift tables will be produced for selected laboratory parameters. These tables will summarize the number of patients with each baseline NCI CTCAE grade and changes to the worst NCI CTCAE grade during study.

Descriptive statistics for the actual values of vital signs and weight over time will be tabulated by scheduled time point. All concomitant medications collected from the first dose throughout the study period will be summarized by preferred term according to the World Health Organization Drug Dictionary.

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point including any unscheduled measurements.

Eastern Cooperative Oncology Group Performance Status and change from baseline will be summarized. Shifts from baseline to the worst postbaseline score will be tabulated by treatment arm.

Additional safety analyses may be determined at any time without prejudice to most clearly enumerate rates of toxicities and to further define the safety profile of study drugs.

8.1.11 Interim Analysis

There are 2 to 3 formal interim analyses included in Phase 2 of the study.

First Interim Analysis

The first interim analysis will be performed when the first 50 events are observed.

Second Interim Analysis

The second interim analysis will be performed when the first 55 events for overall patients with NSCLC (if addition of 20 patients recommended at first interim analysis) or 50 events for patients with squamous or nonsquamous NSCLC (if addition of 20 patients is not recommended at first interim analysis) are observed.

Third Interim Analysis

The third interim analysis will be performed when 50 events for patients with squamous or nonsquamous NSCLC (if addition of 20 patients is recommended at first interim analysis) or 50 events for patients with *PIK3CA* MUT/AMP squamous NSCLC (if addition of 20 patients is not recommended at first interim analysis) are observed.

Final Analysis (if applicable)

The final analysis (if needed) will occur when the 50 events for patients with *PIK3CA* MUT/AMP squamous NSCLC are observed.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event Definition

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

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

9.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[11] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to

function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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

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

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

SAE Reporting Contact Information

[redacted]
Toll-Free Fax #: [redacted]
E-mail: [redacted]

All Other Countries (Rest of World)
Fax #: [redacted]
E-mail: [redacted]

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

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[11] The criteria are provided in the Study Manual.

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

9.3 Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported from the start of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.
- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 9.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 9.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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 expedited reports 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 Good Clinical Practice

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

10.2 Data Quality Assurance

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

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

10.3 Electronic Case Report Form Completion

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

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

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

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

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

10.4 Study Monitoring

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

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

10.5 Ethical Considerations

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

10.6 Patient Information and Informed Consent

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

10.7 Patient Confidentiality

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

10.8 Investigator Compliance

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

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if

circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

10.9 On-site Audits

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

10.10 Investigator and Site Responsibility for Drug Accountability

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

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

10.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints or Medication Errors:
[redacted]
US: [redacted]
International: [redacted] (not toll-free)
Email: [redacted]
Fax: [redacted] (international; not toll-free)

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

10.12 Closure of the Study

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

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

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

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

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

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

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

10.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last

marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

11. USE OF INFORMATION

All information regarding MLN1117 supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN1117 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

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

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

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

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

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

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

12. INVESTIGATOR AGREEMENT

I have read Protocol MLN1117-1501 Amendment 1: A Phase 1b/Adaptive Phase 2 Study of Docetaxel With or Without MLN1117 in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer

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 Eastern Cooperative Oncology Group Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, et al. 1982.[16]

14.2 Cockcroft-Gault Estimate

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

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.[17]

14.3 List of Strong Inhibitors and Inducers of CYP3A4

Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort

Source: fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#cypEnzymes.

14.4 New York Heart Association Classification of Cardiac Disease

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[18]

14.5 Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

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

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - injectable
  - implantable [2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]

- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence [4]

Methods that are Considered Less Highly Effective

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

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]

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

(1) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
(2) Contraception methods that in the context of this guidance are considered to have low user dependency.
(3) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.
(4) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
(5) A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Biostatistics Approval	19-Oct-2015 13:08
[redacted]	Clinical Pharmacology Approval	19-Oct-2015 13:26
[redacted]	Clinical Approval	20-Oct-2015 13:41