Title: A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A-Mediated Inhibition on the Pharmacokinetics, Safety, and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

NCT Number: NCT02122770

Protocol Approve Date: 12 April 2017

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

- Named persons or organizations associated with the study.
- 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.

CLINICAL STUDY PROTOCOL C15011 AMENDMENT 2

MLN4924

A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A-Mediated Inhibition on the Pharmacokinetics, Safety, and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

Protocol Number:	C15011
Indication:	Advanced solid tumors
Phase:	1
Sponsor:	Millennium Pharmaceuticals, Inc.
Therapeutic Area:	Oncology

Protocol History

Original	03 February 2014
Amendment 1	26 February 2015
Amendment 2	12 April 2017

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

PPD Date

PPD Date

PPD Date

Rationale for Amendment 2

The original protocol was written in 2014 and was designed with procedures and assessments requiring many visits. As of 24 February 2017, a total of 3 patients with advanced solid tumors remain on treatment after completion of at least 12 cycles. The sponsor and investigators have therefore determined, on the basis of the accumulated experience to date, that it is appropriate at this time to reduce the frequency of procedures and clinic visits with the intention of lessening patient burden, increasing patient retention, and more closely aligning with clinical practice. Therefore, the primary reason for Amendment 2 is to add flexibility to relieve treatment fatigue for the 3 patients remaining in this study beyond the initially planned 12 cycles of treatment.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes, the rationale for each change, and where the changes are located, see Section 15.12.

Changes in Amendment 2

After completion of Cycle 12, the following changes will be applicable:

1. Extend the 2-day window for scheduling issues (eg, inclement weather, holidays, vacations, or other administrative reasons) to 2 weeks; treatment breaks of up to 4 weeks may be permitted after discussion between the investigator and the project clinician or designee, and the investigator will confirm patient eligibility for continued treatment upon return, before treatment.
2. Reduce the frequency of disease response assessments from every 3 cycles to every 6 cycles.
3. Reduce the frequency of hematology, vital sign, clinical chemistry, and electrocardiogram assessments and physical examinations.
4. Add phosphate to the urinalysis parameters.
5. Add a ±10-minute window to the MLN4924 infusion duration.
6. Remove the requirement for independent data monitoring committee monitoring.
7. Adjust contraception requirements to be consistent with Clinical Trial Facilitation Group recommendations.
8. Update the description of the drug product.
9. Update the investigator responsibilities for compliance with updated International Conference on Harmonisation guidelines.
10. Update the description of dose-limiting toxicities observed in Study C15003 to be consistent with final data.
11. Update vital signs assessments to allow measurements to be taken with the patient in the supine or sitting position.
12. Clarify the timing of transfusion for red blood cells to at least 1 day before study drug administration.

13. Remove gamma glutamyl transferase from the serum chemistry parameters.
14. Remove known breast cancer resistance protein substrates, moderate and strong inhibitors of cytochrome P450 3A4, and inhibitors of P-glycoprotein from the list of excluded concomitant medications.
15. Replace references to the Safety Management Attachment with references to the Development Core Safety Information.
16. Update the description of the Safety Management Team to be consistent with current preferred language and to reflect its cross-functional nature.
17. Update contact information for product complaints.

PROTOCOL SUMMARY

Study Title: A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A-Mediated Inhibition on the Pharmacokinetics, Safety, and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

Number of Patients: Up to approximately 52 patients

Study Objectives

Primary

- To assess the effect of multiple-dose administration of fluconazole, a moderate cytochrome P450 (CYP) 3A inhibitor, on the single-dose intravenous (IV) pharmacokinetics (PK) of MLN4924
- To assess the effect of multiple-dose administration of itraconazole, a strong CYP3A inhibitor, on the single-dose IV PK of MLN4924

Secondary

Part A

- To further evaluate the safety and tolerability of MLN4924
- To further describe the IV PK of MLN4924 before and after multiple oral dosing with fluconazole or itraconazole

Part B

- To further assess the safety and tolerability of MLN4924 in combination with docetaxel in patients with solid tumors
- To further assess the safety and tolerability of MLN4924 in combination with carboplatin and paclitaxel in patients with solid tumors
- To further evaluate disease response that may be observed with the combination of MLN4924 and docetaxel
- To further evaluate disease response that may be observed with the combination of MLN4924, carboplatin, and paclitaxel

Exploratory

Part A

CCI [redacted]

Overview of Study Design: This is an open-label, multicenter, parallel group, 2-arm, phase 1 study of MLN4924 designed to assess drug-drug interactions (DDIs) with the moderate and strong CYP3A inhibitors fluconazole and itraconazole, respectively, in patients with advanced solid tumors. In the Fluconazole Arm, approximately 12 PK-evaluable patients will be enrolled. In the Itraconazole Arm, approximately 12 PK-evaluable patients will be enrolled in the 8-mg/m^2 and 20-mg/m^2 MLN4924 cohorts, and 3 additional PK-evaluable patients will be needed in the safety lead-in cohort.

Part A: Drug-Drug Interaction Assessment

Fluconazole Arm: Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This low dose of MLN4924 is anticipated to provide an adequate safety margin for DDI assessment. Patients will receive concomitant oral fluconazole at a dose starting at 400 mg on Day 4 and then 200 mg once daily on Days 5 through 10. Pharmacokinetic samples will be taken after the MLN4924 dose on Day 1 and after the Day 8 dose of MLN4924 with fluconazole at predetermined time points to assess the effect of fluconazole on the PK of MLN4924. Additional samples for determination of MLN4924 concentrations in whole blood will be collected on Day 1 only.

Itraconazole Arm: Patients will receive a single dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8 (see dose cohorts defined below). Patients will receive concomitant oral itraconazole at a dose of 200 mg once daily on Days 4 through 10. Pharmacokinetic samples will be taken after the MLN4924 dose on Day 1 and after the Day 8 dose of MLN4924 with itraconazole at predetermined time points (up to 72 hours after dosing) to assess the effect of itraconazole on the PK of MLN4924. Additional samples for determination of MLN4924 concentrations in whole blood will be collected on Day 1 only. The following dose cohorts will be enrolled sequentially within the Itraconazole Arm:

- Itraconazole Arm, 8-mg/m^2 MLN4924 Cohort: Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This low dose of MLN4924 is anticipated to provide an adequate safety margin for DDI assessment.
- Itraconazole Arm, Safety Lead-in 15-mg/m^2 MLN4924 Cohort: Patients will receive a single 15-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. Data from this safety lead-in cohort will confirm the anticipated safety margin is adequate before any patients are enrolled in the 20-mg/m^2 MLN4924 cohort.
- Itraconazole Arm, 20-mg/m^2 MLN4924 Cohort: Patients will receive a single 20-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This dose of MLN4924 falls within the clinically relevant dose range currently evaluated in Phase 1b combination studies of MLN4924 plus standard of care therapies.

Patients will be required to visit the clinic on Day 4 for their first dose of fluconazole or itraconazole. For both the Fluconazole and Itraconazole Arms, all doses of fluconazole and itraconazole will be administered on an empty stomach with the patient fasting from food and fluids, except water and prescribed medications, for 2 hours before and 1 hour after each dose. Patients are encouraged to take fluconazole or itraconazole doses at approximately the same time each morning and approximately 24 hours apart. On Day 8, patients will take fluconazole or itraconazole together with MLN4924 in the morning at the clinic.

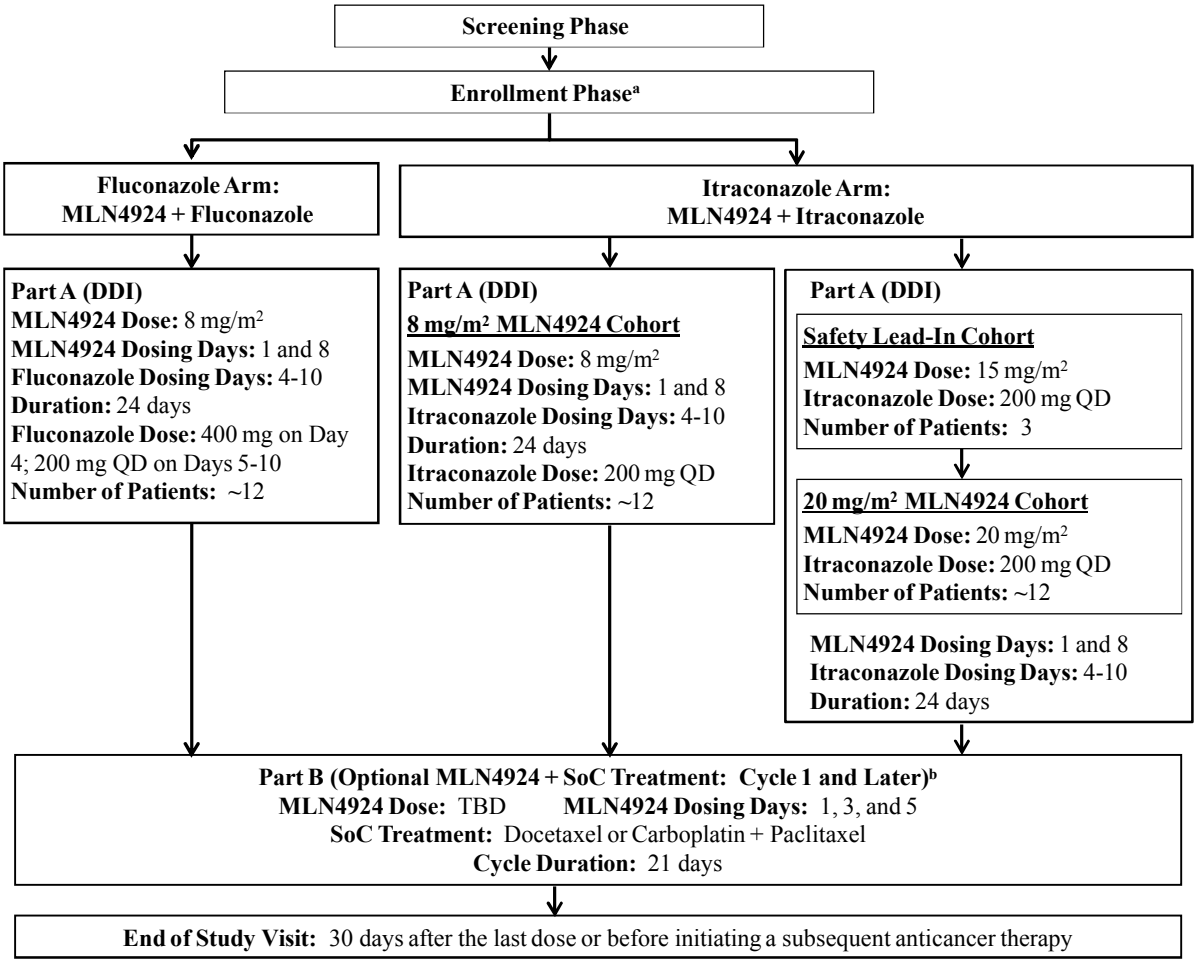
In addition to blood sampling for PK, blood samples in the 24-hour postdose window of each arm following dosing on Day 1 and Day 8 will be collected to measure pharmacodynamic effects of MLN4924. These data will be pooled with data from other MLN4924 clinical studies to contribute to an integrated PK-pharmacodynamic analysis across the program.

Part B: Continued Treatment With MLN4924 in Combination With Standard of Care

After completion of the DDI assessment portion of the study, patients will have the opportunity to continue in the study by participating in Part B. Patients will receive MLN4924 in combination with either docetaxel or carboplatin+paclitaxel at a dose regimen informed from Study C15010 that has been deemed tolerable (eg, no dose-limiting toxicities [DLTs] in 3 patients or no more than 1 DLT in 6 patients). The selected dose may be adjusted based on information obtained from the ongoing review of safety data. Safety and disease assessments will be conducted in Part B of the study.

Study Population: Patients 18 years of age or older who have a histologically or cytologically confirmed metastatic or locally advanced solid tumor that is deemed appropriate for treatment with 1 of the 2 chemotherapy regimens in Part B of this study, or who have progressed despite standard therapy, or for whom conventional therapy is not considered effective.
Duration of Study: Patients participating in Part B will be treated (after at least a 2-week [and up to 8-week] washout period after receiving their last dose of fluconazole or itraconazole in Part A) until they experience symptomatic deterioration or progressive disease, or until their treatment is discontinued for another reason, or until the study is stopped. After completion of at least 12 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued treatment (Section 6.4.2) upon return from a treatment break, before treatment.

STUDY OVERVIEW DIAGRAM 1

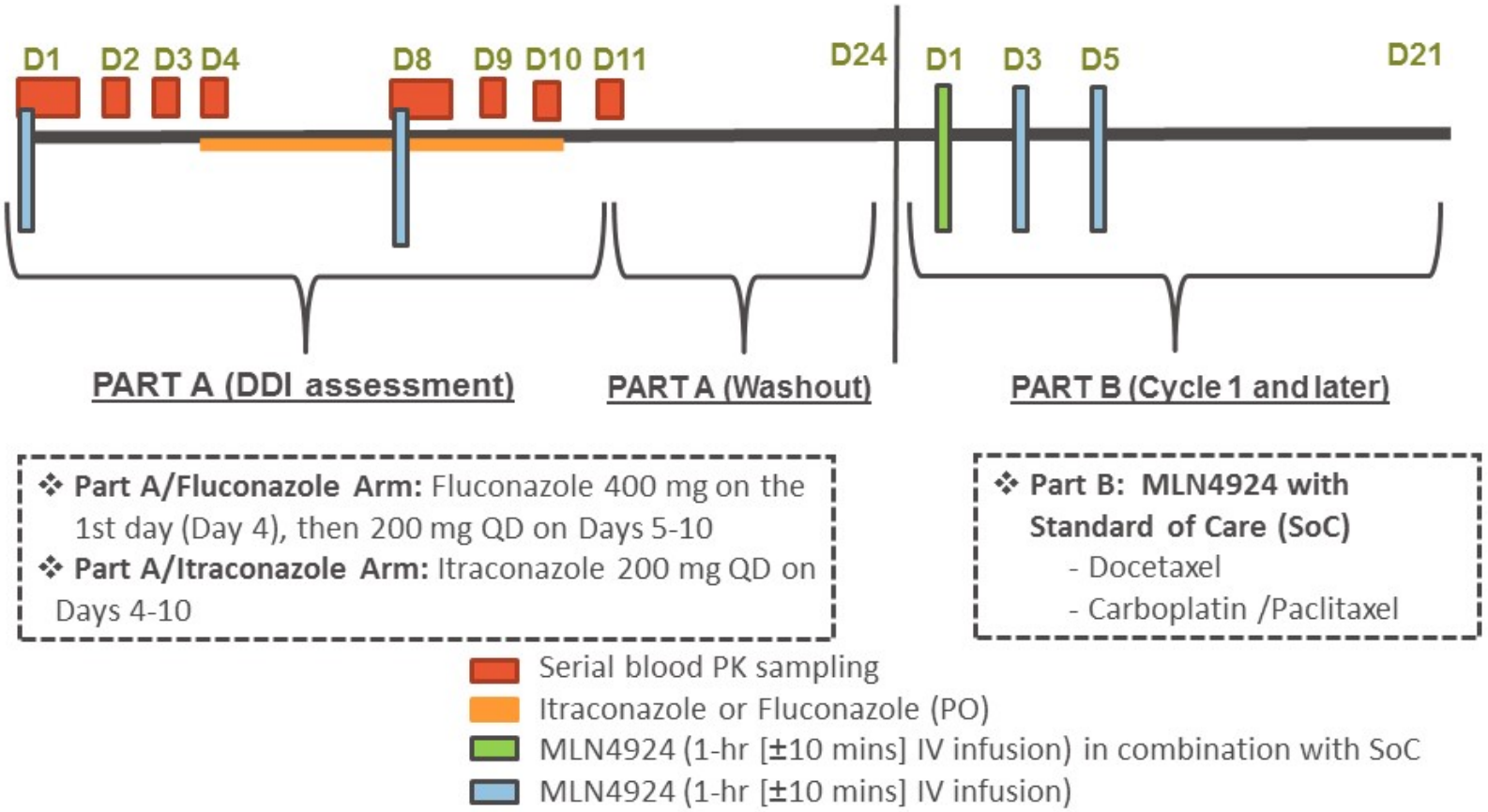


Abbreviations: DDI=drug-drug interaction; QD=once daily; SoC=standard of care; TBD=to be determined

a The first 4-8 patients will be assigned to the Fluconazole Arm (moderate CYP3A inhibitor), then following review of the emerging data, patients will be assigned to both the Fluconazole Arm and the Itraconazole Arm, 8-mg/m^2 MLN4924 Cohort in parallel based on slot availability. Enrollment into the Itraconazole Arm, Safety Lead-in 15-mg/m^2 MLN4924 Cohort, added per Amendment 1, may begin once the amendment is approved at the clinical site. Enrollment into the Itraconazole Arm, 20-mg/m^2 MLN4924 Cohort may begin once the Part A PK and safety data from 3 PK-evaluable patients in the safety lead-in cohort have been reviewed and the sponsor has confirmed that the anticipated safety margin for the 20-mg/m^2 dose is adequate.

b After completing Part A, the patient will be re-evaluated to meet entry criteria to participate in Part B.

STUDY FLOW DIAGRAM 2



Abbreviations: D=Day; DDI=drug-drug interaction; IV=intravenous; QD=once daily; PO=oral.
Note: As of Amendment 2, a ±10-minute window will be applied to the MLN4924 IV infusion time.

SCHEDULES OF EVENTS

Schedule of Events for Drug-Drug Interaction (Part A)

	Baseline	Treatment Period								Washout	
		Week 1					Week 2				Week 3	
	Screening[a]	Day 1 Predose	Day 1	Day 2	Day 4	Days 5-7[b]	Day 8 Predose	Day 8	Days 9-10[c]	Day 11	Day 24[d]	End of Study[e]
Study Drug Administration												
MLN4924 administration[f]			X					X[g]				
CYP3A inhibitor administration[h]					X	X[i]		X[g]	X			
Provide and review patient diary[j]					X		X					
Study Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Medical history/prior therapy	X											
Full physical examination	X										X	X
Symptom-directed physical examination		X		X	X		X		X	X		
Height	X											
Weight	X	X[k]									X	
Vital signs[l]	X	X[k]	X	X	X		X	X	X	X	X	X
ECOG performance status	X	X[k]									X	X

Schedule of Events for Drug-Drug Interaction (Part A)

	Baseline	Treatment Period									Washout	
		Week 1					Week 2				Week 3	
	Screening[a]	Day 1 Predose	Day 1	Day 2	Day 4	Days 5-7[b]	Day 8 Predose	Day 8	Days 9-10[c]	Day 11	Day 24[d]	End of Study[e]
12-lead ECG[m]	X	X[k]	X				X	X		X	X	X
Echocardiogram	X											
Adverse event reporting		Recorded from first dose of study drug through 30 days (+ 10 days) after the last dose of study drug										
	Serious adverse events will be reported from signing of the informed consent form through 30 days (+ 10 days) after the last dose of study drug.											
Concomitant medications, therapies, and procedures		Recorded from first dose of study drug through 30 days (+ 10 days) after the last dose of study drug										
Laboratory Assessments												
Pregnancy test	X											
Hematology[n]	X	X[k]		X	X		X		X	X	X	X
Clinical chemistry panel[o]	X	X[k]	X	X	X		X	X	X	X	X	X
Coagulation[p]	X	X[k]										
Urinalysis with microscopic analysis[q]	X	X[k]					X			X	X	X
Blood sample for PK[r]		X					X					
Blood sample for PD[s]	X						X					

Abbreviations: aPTT=activated partial thromboplastin time; CYP=cytochrome P450; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=End of Study; INR=international normalized ratio; IV=intravenous; PD=pharmacodynamic(s); PK=pharmacokinetic(s); PT=prothrombin time; SoC=standard of care.

a Unless otherwise noted, the Screening visit must occur within 28 days before the day of the first dose of study drug in Part A.

b Study Days 5-7 are patient home dosing days, and no visit to the clinic is required.

c Each assessment is to occur on Day 9 and on Day 10.

d Patients will require at least a 2-week (and up to 8-week) drug washout period after their last dose of fluconazole or itraconazole (SPORANOX®) in Part A before starting Part B (dosing with MLN4924+SoC). The Day 24 visit should occur on Day 24 (+ 2 days). For patients to be eligible for dosing in Part B, they

Schedule of Events for Drug-Drug Interaction (Part A)

	Baseline	Treatment Period									Washout	
		Week 1					Week 2				Week 3	
	Screening[a]	Day 1 Predose	Day 1	Day 2	Day 4	Days 5-7[b]	Day 8 Predose	Day 8	Days 9-10[c]	Day 11	Day 24[d]	End of Study[e]

must meet certain entry criteria; refer to Section 7.4.20. If the criteria in Section 7.4.20 are met on Day 24 of Part A, the patient will be eligible for Part B dosing immediately. If the criteria in Section 7.4.20 are NOT met on Day 24, see footnote a in the Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 1 Through Cycle 12 for requirements to begin Part B dosing.

e An EOS visit is needed in Part A only if the patient does not continue into Part B. The EOS visit will occur 30 days (+ 10 days) after the last dose of study drugs or before the start of subsequent therapy for their indication, if that occurs sooner.

f MLN4924 will be administered via a 1-hour (± 5 minutes) IV infusion. If during Part A there is a need to interrupt or slow the IV infusion, refer to Section 6.1.1.

g On Day 8, when the CYP3A inhibitor (fluconazole or itraconazole) and MLN4924 are given together, the CYP3A inhibitor (fluconazole or itraconazole) is to be given first, followed by the 1-hour (± 5 minutes) IV infusion of MLN4924 approximately 20 minutes (±10 min) after ingestion of the fluconazole tablet or itraconazole oral solution.

h Fluconazole and itraconazole are the CYP3A inhibitors used in Part A of the study. **All doses of study drug(s) will be administered on an empty stomach.** The first dose of fluconazole (400 mg as two 200-mg tablets) or itraconazole (200 mg as oral solution) will be administered in the clinic by a qualified study team member on the morning of Day 4 after collection of the 72-hour PK sample. A qualified study team member will also administer the oral dose of fluconazole (one 200-mg tablet) or itraconazole (200 mg as oral solution) on Day 8 just before the start of the 1-hour (± 5 minutes) IV infusion with MLN4924, and on the morning of Days 9 and 10 after the 24- and 48-hour PK sample collections.

i Patients will self-administer fluconazole (200-mg tablet) or itraconazole (200 mg oral solution) at home. Patients are required to take the CYP3A inhibitor once daily on Days 5, 6, 7 at approximately the same time each day (± 2 hours from time of first dose). If any dose is missed, the subject will not be considered PK evaluable.

j Thorough instructions regarding the fluconazole or itraconazole dosing schedule, study drug handling, use of the patient diary, follow-up visit expectations, and return of study drug containers and unused study drug will be provided on Day 4 before dosing with fluconazole or itraconazole. Study staff are to review all entries in the patient diary on Day 8 before dosing. Study staff will assess patient compliance with at-home dosing on study Day 8 to confirm that the patient will be PK evaluable (see Section 8.1.4).

k Procedures conducted during screening that are performed within 3 days of Day 1 can also be used as the Day 1 predose evaluation and do not need to be repeated.

l Vital signs are to be measured predose (20 minutes [± 10 min]) before the infusion of MLN4924; 30 minutes (± 10 min) after the start of MLN4924 dosing; and 1 hour (± 10 min) and 3 hours (± 30 min) after the completion of MLN4924 dosing. All vital signs are measured with the patient in the sitting position. In addition, at predose and 1 hour postdose of MLN4924 administration on Day 1 and Day 8, **orthostatic** blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting approximately 3-4 minutes. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

Schedule of Events for Drug-Drug Interaction (Part A)

	Baseline	Treatment Period									Washout	
		Week 1					Week 2				Week 3	
	Screening[a]	Day 1 Predose	Day 1	Day 2	Day 4	Days 5-7[b]	Day 8 Predose	Day 8	Days 9-10[c]	Day 11	Day 24[d]	End of Study[e]

m A 12-lead ECG will be performed during screening and before administration (within 3 hours) of MLN4924 on Day 1 and Day 8 and immediately after the MLN4924 infusion is complete (± 20 min) on Day 1 and Day 8. When the timing of ECG measurements coincides with the timing of a blood draw, the ECG will be completed before the blood sample collection, with the exception of the end-of-infusion PK sample, which should be collected before the ECG is completed.

n Hematology samples will be collected during screening and before dosing with study drug on Days 1 and Day 8. These samples may be drawn with 24 hours predose. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. In addition, samples will be taken on Days 2, 4, 9, 10, 11, and 24 and at the EOS visit.

o Clinical chemistry samples will be collected during screening, before dosing with study drug, and 3 hours (± 30 min) after completion of the MLN4924 infusion. These predose samples can be drawn within 24 hours predose. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. In addition, samples will be taken on Days 2, 4, 9, 10, 11, and 24 and at the EOS visit.

p A coagulation panel at screening will include the following: PT (INR), aPTT, fibrinogen, and D-dimer.

q Urinalysis samples will be analyzed at the site's local laboratory.

r See the Serial Pharmacokinetic Sample Breakdown for all PK collection times. During Part A of the study, serial blood sampling will be collected from each patient for determination of plasma concentrations of MLN4924 following MLN4924 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. Additionally, limited blood sampling for determination of MLN4924 content in whole blood will be performed on Day 1.

s See the Serial Pharmacodynamic Sample Breakdown for all pharmacodynamic collection times.

Serial Pharmacokinetic Sample Breakdown: Drug-Drug Interaction Cycle (Part A)

Study Day/Time	Day 1	Day 2	Day 3	Day 4	Day 8[a]	Day 9[a]	Day 10[a]	Day 11
Predose[b]	X				X			
End of infusion (EOI) (– 5 to + 1 min)[c,d]	X[e]				X			
0.5 hour postinfusion (± 5 min)[f]	X				X			
1 hour postinfusion (± 15 min)[d,f]	X				X			
2 hours postinfusion (± 15 min)[f]	X[e]				X			
3 hours postinfusion (± 30 min)[d,f]	X				X			
4 hours postinfusion (± 45 min)[f]	X				X			
8 hours postinfusion (± 1 hour)[f]	X[e]				X			
12 hours postinfusion (± 1 hour)	X				X			
24 hours postdose (± 1 hour)[g]		X[e]				X		
48 hours postdose (± 2 hours)[g]			X				X	
72 hours postdose (± 3 hours)[g]				X				X

Abbreviations: ECG=electrocardiogram; IV=intravenous; min=minutes; PK=pharmacokinetic(s).

a Patients should be instructed to come to the clinic in the morning without taking their morning doses of study drug(s). All doses of study drug(s) will be administered on an empty stomach.

b The sample is to be collected within 1 hour before the start of MLN4924 infusion.

c The window for collection of the EOI time point is between 5 minutes before completion of the infusion to 1 minute after completion of the infusion. If the IV infusion is interrupted, 2 additional PK samples (1 sample drawn when the infusion is stopped and 1 sample drawn when the infusion is restarted) should be collected so that the patient may be considered PK evaluable. Please refer to Section 6.1.1 if the IV infusion needs to be interrupted or slowed.

d When the timing of a blood draw coincides with the timing of vital signs or ECG measurements, the vital signs or ECG will be completed before the blood sample collection, with the exception of the EOI sample, which should be collected before the ECG is completed. Full details of PK sample preparation will be provided in the Study Manual.

e Sampling for determination of MLN4924 concentrations in whole blood. Full details of PK sample preparation will be provided in the Study Manual.

f Samples are to be collected after **the completion** of MLN4924 IV infusion.

g Samples are to be collected 24 (± 1 hour), 48 (± 2 hours), and 72 (± 3 hours) hours **after initiation** of the MLN4924 IV infusion on Day 1 (or Day 8).

Serial Pharmacodynamic Sample Breakdown: Drug-Drug Interaction Cycle (Part A)

Study Day/Time	Screening	Day 1	Day 2	Day 8[a]	Day 9[a]
Predose[b]	X	X		X	
1 hour postinfusion (± 15 min)[c,d]		X		X	
4 hours postinfusion (± 45 min)[d]		X		X	
8 hours postinfusion (± 1 hour)[d]		X		X	
24 hours postdose (± 1 hour)[e]			X		X

Abbreviations: ECG=electrocardiogram; min=minutes.

At each time point, 2 blood samples will be taken to enable 2 independent sets of pharmacodynamics assays to be performed. Full details of sample preparation will be provided in the Study Manual.

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

b The sample is to be collected within 1 hour before the start of MLN4924 infusion.

c When the timing of a blood draw coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

d Samples are to be collected after **the completion** of the MLN4924 IV infusion.

e Sample is to be collected 24 hours **after initiation** of the MLN4924 IV infusion on Day 1 (or Day 8).

Patients are assessed for eligibility to participate in Part B only after completion of Part A and anytime during the 2- to 8-week washout period.

Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 1 Through Cycle 12

	MLN4924+SoC Treatment						End of Study/ Early Termination[c]
	Day 1 Predose[a]	Day 1	Day 2[b]	Day 3	Day 5	Day 8	
Study Drug Administration							
SoC administration[d]		X					
MLN4924 administration[d]		X		X	X		
Study Procedures							
Physical examination	X						X
Symptom-directed physical examination			X	X	X	X	X
ECOG performance status	X						X
Weight	X						X
Vital signs[e]	X	X	X	X	X	X	X
12-Lead ECG[f]	X	X					
Tumor assessments[g]	To be completed before dosing in Part B, end of Cycle 2, end of Cycle 4, and every other cycle thereafter						X
Concomitant medications, therapies and procedures	Recorded from first dose of study drug in Part A through 30 days (+ 10 days) after the last dose of study drug in Part B						
Adverse event reporting	Recorded from first dose of study drug in Part A through 30 days (+ 10 days) after the last dose of study drug in Part B						
	Serious adverse events will be reported from signing of the informed consent form through 30 days (+ 10 days) after the last dose of study drug						
Laboratory Assessments							
Hematology[h]	X		X	X	X	X	X
Clinical chemistry panel[i]	X	X[j]	X	X	X	X	X
Coagulation[k]	X						

Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 1 Through Cycle 12

	MLN4924+SoC Treatment						End of Study/ Early Termination[c]
	Day 1 Predose[a]	Day 1	Day 2[b]	Day 3	Day 5	Day 8	
Urinalysis with microscopic analysis[l]	X			X	X		X

Abbreviations: aPTT=activated partial thromboplastin time; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=End of Study; INR=international normalized ratio; MRI=magnetic resonance imaging; PT=prothrombin time; SoC=standard of care.

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

a For patients to be eligible for dosing with MLN4924+SoC (Part B), they must meet certain entry criteria (see Section 7.4.20). If, at the end of Part A, the patient is eligible for dosing in Part B, the Day 24 assessments in Part A could be used as the Part B predose Cycle 1, Day 1 assessments if Cycle 1, Day 1 occurs within 5 days of Day 24 in Part A; however, the liver function tests will need to be repeated within 3 days of Cycle 1, Day 1. The washout period may be extended up to 6 additional weeks to allow more time for patients to recover and qualify for Part B. The patient should be assessed at least every 2 weeks for eligibility for Part B during this extended washout period. The patient can be deemed eligible for Part B anytime during the 2- to 8-week washout period. If, after 8 weeks from the last dose in Part A (eg, up to 8 weeks after the Day 10 visit), the predose Cycle 1, Day 1 assessments for Part B have not returned to Part A baseline values (or ≤ Grade 1) or to a level considered acceptable by the investigator after discussion with the project clinician or designee, then the patient will not be eligible for dosing with MLN4924+SoC, and all assessments required for the EOS visit should be completed.

b The assessments conducted on Day 2 are required only during Cycle 1.

c If the patient continues into Part B, the EOS visit will occur 30 days (+ 10 days) after the last dose of study drug(s) in Part B or before the start of subsequent therapy for their indication, if that occurs sooner.

d The investigator will select which SoC chemotherapy (docetaxel or carboplatin+paclitaxel) that each patient will receive in combination with MLN4924. On Day 1, when MLN4924 and chemotherapy agents are both administered, chemotherapy will be administered first, followed by MLN4924. The infusion of MLN4924 may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of MLN4924 may be reduced because of toxicities in accordance with Section 6.4. The chemotherapeutic agent may be dose reduced because of toxicities in accordance with Section 6.4. See Section 6.1 for the details of study drug administration. **NOTE: a time-out of approximately 15 minutes is required between the end of infusion of the chemotherapy regimen and the start of infusion of MLN4924.**

e Vital signs are to be measured predose (20 minutes [± 10 min]) before the infusion of MLN4924; 30 minutes (± 10 min) after start of MLN4924 dosing; and 1 hour (± 10 min) after completion of MLN4924 dosing. All vital signs are measured with the patient in the sitting position. In addition, at predose and 1 hour postdose of MLN4924 administration on Cycle 1, Day 1, **orthostatic** blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting for approximately 3-4 minutes. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

f A 12-lead ECG will be performed on Day 1 before administration (within 3 hours) of the chemotherapy regimen and immediately after the infusion of MLN4924 is complete (± 10 min). When the timing of ECG measurements coincides with the timing of a blood draw, the ECG will be completed before the collection of the blood sample, with the exception of the end of infusion PK sample which should be taken before the ECG is completed.

g Radiological evaluations (CT scan or MRI) of the chest, abdomen, and pelvis will be required as entry criteria for Part B to assess the status of the patient's

Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 1 Through Cycle 12

	MLN4924+SoC Treatment						End of Study/ Early Termination[c]
	Day 1 Predose[a]	Day 1	Day 2[b]	Day 3	Day 5	Day 8	

underlying disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1, Day 1 of Part B, then the results of those scans may be used. During the study, CTs or MRIs encompassing the known sites of disease will be performed at the end of Cycle 2, end of Cycle 4, and at the end of every other cycle thereafter. An end of study/early termination CT scan does not need to be completed/repeated if a scan was performed within the previous 28 days.

h Hematology samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. On dosing days, samples can be drawn 24 hours predose. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. In addition, samples will be taken on Day 2 (Cycle 1 only), Day 8, and at the EOS visit.

i Clinical chemistry samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. On Days 1, 3, and 5, samples may be drawn within 24 hours predose. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. On Cycle 1, Day 1 an additional sample will be taken 3 hours (± 30mins) after completion of the MLN4924 infusion. In addition, samples will be taken on Day 2 (Cycle 1only), Day 8, and at the EOS visit.

j The Day 1 postdose clinical chemistry assessment is required only during Cycle 1.

k A coagulation panel at screening for Part A will include the following: PT (INR), aPTT, fibrinogen, and D-dimer. If the initial coagulation screen in Part A is positive (ie, results are outside of the laboratory's normal range), subsequent coagulation studies in Part B should include all of these parameters. If the initial coagulation screen in Part A is negative (ie, results are within the laboratory's normal range), no further coagulation studies need to be done.

l Urinalysis samples will be analyzed at the site's local laboratory.

Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 13 and Beyond (as of Amendment 2)

	MLN4924+SoC Treatment				End of Study/ Early Termination[b]
	Day 1 Predose[a]	Day 1	Day 3	Day 5	
Study Drug Administration					
SoC administration[c]		X			
MLN4924 administration[c]		X	X	X	
Study Procedures					
Symptom-directed physical examination	X				X
ECOG performance status	X				X
Weight	X				X
Vital signs[d]	X	X	X	X	X
12-Lead ECG[e]	X				
Tumor assessments[f]	To be performed after completion of every sixth cycle after the patient's previous scan				X
Concomitant medications, therapies and procedures	Recorded from first dose of study drug in Part A through 30 days (+ 10 days) after the last dose of study drug in Part B				
Adverse event reporting	Recorded from first dose of study drug in Part A through 30 days (+ 10 days) after the last dose of study drug in Part B				
	Serious adverse events will be reported from signing of the informed consent form through 30 days (+ 10 days) after the last dose of study drug				
Laboratory Assessments					
Hematology[g]	X		X	X	X
Clinical chemistry panel[h]	X		X	X	X
Coagulation[i]	X				
Urinalysis with microscopic analysis[j]	X		X	X	X

Abbreviations: aPTT=activated partial thromboplastin time; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology

Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 13 and Beyond (as of Amendment 2)

	MLN4924+SoC Treatment				End of Study/ Early Termination[b]
	Day 1 Predose[a]	Day 1	Day 3	Day 5	

Group; EOS=End of Study; INR=international normalized ratio; MRI=magnetic resonance imaging; PK=pharmacokinetic; PT=prothrombin time; SoC=standard of care.

Tests and procedures should be performed on schedule, but occasional changes are allowable (± 2 days) for holidays, vacations, and other administrative reasons. After implementation of Amendment 2 and completion of Cycle 12, modifications of up to 2 weeks (up to 4 weeks after consulting with the sponsor) are permitted, at the investigator's discretion; treatment breaks may not be taken consecutively.

a For patients who take treatment breaks at the investigator's discretion, patient eligibility for continued treatment, including all Day 1 predose assessments, will be confirmed by the investigator before resumption of treatment.

b If the patient continues into Part B, the EOS visit will occur 30 days (+ 10 days) after the last dose of study drug(s) in Part B or before the start of subsequent therapy for their indication, if that occurs sooner.

c The investigator will select which SoC chemotherapy (docetaxel or carboplatin+paclitaxel) that each patient will receive in combination with MLN4924. On Day 1, when MLN4924 and chemotherapy agents are both administered, chemotherapy will be administered first, followed by MLN4924. The infusion of MLN4924 may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of MLN4924 may be reduced because of toxicities in accordance with Section 6.4. The chemotherapeutic agent may be dose reduced because of toxicities in accordance with Section 6.4. See Section 6.1 for the details of study drug administration. **NOTE: a time-out of approximately 15 minutes is required between the end of infusion of the chemotherapy regimen and the start of infusion of MLN4924.**

d Vital signs are to be measured predose (20 minutes [± 10 min]) before the infusion of MLN4924; 30 minutes (± 10 min) after start of MLN4924 dosing; and 1 hour (± 10 min) after completion of MLN4924 dosing. All vital signs are measured with the patient in either the sitting or supine position. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

e A 12-lead ECG will be performed on Day 1 before administration (within 3 hours) of the chemotherapy regimen and immediately after the infusion of MLN4924 is complete (± 10 min). When the timing of ECG measurements coincides with the timing of a blood draw, the ECG will be completed before the collection of the blood sample, with the exception of the end of infusion PK sample which should be taken before the ECG is completed.

f Radiological evaluations (CT scan or MRI) of the chest, abdomen, and pelvis will be required as entry criteria for Part B to assess the status of the patient's underlying disease. CTs or MRIs encompassing the known sites of disease will be performed after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 2). Additional CT scans may be performed, per investigator's discretion, if clinically indicated. An end of study/early termination CT scan does not need to be completed/repeated if a scan was performed within the previous 28 days.

g Hematology samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. On dosing days, samples can be drawn within 24 hours predose. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. In addition, samples will be taken at the EOS visit.

h Clinical chemistry samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. On Days 1, 3, and

Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 13 and Beyond (as of Amendment 2)

	MLN4924+SoC Treatment				End of Study/ Early Termination[b]
	Day 1 Predose[a]	Day 1	Day 3	Day 5	

5, samples may be drawn within 24 hours predose. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. In addition, samples will be taken at the EOS visit.

i A coagulation panel at screening for Part A will include the following: PT (INR), aPTT, fibrinogen, and D-dimer. If the initial coagulation screen in Part A is positive (ie, results are outside of the laboratory's normal range), subsequent coagulation studies in Part B should include all of these parameters. If the initial coagulation screen in Part A is negative (ie, results are within the laboratory's normal range), no further coagulation studies need to be done.

j Urinalysis samples will be analyzed at the site's local laboratory.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
ACS	acute coronary syndrome
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}24\ hr}$	AUC from time zero to 24 hours
$AUC_{0\text{-}inf}$	AUC from time zero to infinity
$AUC_{0\text{-}tlast}$	AUC from time zero to the time of the last quantifiable concentration
BCRP	breast cancer resistance protein
B/P	blood to plasma ratio
BSA	body surface area
BUN	blood urea nitrogen
CD	compact disk
CDL	cullin-dependent ubiquitin E3 ligases
Cdt-1	chromatin-licensing and DNA-replication factor-1
CHF	congestive heart failure
CI	confidence intervals
CL	clearance
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CR	complete response
CSR	clinical study report
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450

Abbreviation	Term
DCSI	Development Core Safety Information
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GI	gastrointestinal
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IIV	interindividual variability
IRB	institutional review board
IV	intravenous; intravenously
LDH	lactate dehydrogenase
LFT	liver function test(s)
MDS	myelodysplastic syndromes
MI	myocardial infarction
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRP2	multidrug resistance associated protein 2
MTD	maximum tolerated dose

Abbreviation	Term
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDD8	neural precursor cell expressed developmentally down-regulated protein 8
Nrf2	NFE2-related factor 2
NSCLC	nonsmall cell lung cancer
OATP	organic anion-transporting polypeptides
PBMC	peripheral blood mononuclear cell
PD	progressive disease (disease progression)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	prothrombin time
QD	once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCLC	small cell lung cancer
SD	stable disease
SoC	standard of care
SWOG	Southwest Oncology Group
$t_{1/2}$	terminal elimination half-life
T_{max}	first time to achieve maximum observed plasma concentration
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia
USPI	United States Package Insert
V_{ss}	volume distribution

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background of Study Drug

MLN4924 is a first-in-class small molecule inhibitor of the NEDD8 (neural precursor cell expressed developmentally down-regulated protein 8)-activating enzyme (NAE) that is being developed for the treatment of malignancies. NEDD8-activating enzyme is an E1-activating enzyme and is an essential component of the NEDD8 conjugation pathway, which controls the activity of a subset of ubiquitin E3 ligases, multiprotein complexes that transfer ubiquitin molecules to protein substrates that are then targeted to the proteasome for degradation. Cullin-dependent ubiquitin E3 ligases (CDLs) require conjugation to NEDD8 to be activated. Cullin-dependent ubiquitin E3 ligases control the timely ubiquitination and consequent proteasomal degradation of proteins with important roles in cell cycle progression and signal transduction, cellular processes that are integral to tumor cell growth, proliferation, and survival. Inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by disrupting proteasomal degradation of a variety of critical regulatory proteins.

1.2 Nonclinical Experience of Single-agent MLN4924

MLN4924 is a potent and selective inhibitor of NAE activity.

MLN4924 treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines. Changes in protein levels observed in cultured cells treated with MLN4924 were consistent with the inhibition of NAE, in particular a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including NFE2-related factor 2 (Nrf2) and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In most cell lines evaluated, NAE inhibition by MLN4924 led to DNA re-replication and accumulation of cells in the S phase of the cell cycle; this resulted in DNA damage and subsequent cell death through apoptosis.[1, 2, 3]

MLN4924 demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and acute myelogenous leukemia (AML) xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN4924 may be found in the Investigator's Brochure (IB).

1.3 MLN4924 Pharmacokinetics

1.3.1 Nonclinical Pharmacokinetics and Risk Assessment for Drug-Drug Interactions

The absorption, distribution, metabolism, and excretion properties of MLN4924 have been studied in Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and chimpanzees. Hepatic metabolism appears to be the major route of elimination for MLN4924 in animal species. Urinary excretion of unchanged MLN4924 was found to be low (< 5%) in rats and primates.

MLN4924 is metabolized in vitro via hydroxylation oxidation, predominantly by cytochrome P450 (CYP) 3A4 with a small (3%) contribution from CYP2D6. In vitro studies with efflux pump inhibitors demonstrated that MLN4924 is a substrate for P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein 2 (MRP2). However, MLN4924 is a weak inhibitor of P-gp (concentration producing 50% inhibition [IC_{50}] [paclitaxel and digoxin] of 41.2-56.0 μM) and BCRP (IC_{50} [estrone-3-sulfate] of 6.3 μM) but is not likely to inhibit MRP2 (IC_{50} > 200 μM). Additional studies with organic anion-transporting polypeptides (OATP) in sandwich-cultured human hepatocytes showed that MLN4924 can inhibit the hepatic uptake of estrone-3-sulfate (IC_{50} of 29.1 μM) and of simvastatin (IC_{50} of 0.4-4.9 μM) and lovastatin (IC_{50} of 0.9 μM) from some, but not all, donors. Taking these data together and based on observed single-dose maximum (peak) concentration (C_{max}) values at doses ≤ 110 mg/m^2, MLN4924 is unlikely to interact with P-gp substrates, but the potential exists, albeit low, for drug interactions with BCRP and OATP substrates at clinical concentrations.

1.3.2 Clinical Pharmacokinetics

The pharmacokinetics (PK) of MLN4924 administered as an 1-hour intravenous (IV) infusion have been evaluated following single and multiple doses in adult patients with nonhematologic malignancies (Study C15001); adult patients with lymphoma or multiple myeloma (Study C15002); adult patients with AML, high-grade myelodysplastic syndromes (MDS), or acute lymphoblastic leukemia (ALL) (Study C15003); and adult patients with melanoma (Study C15005).

Pharmacokinetic results showed that MLN4924 PK is linear over the dose range studied as evidenced by area under the plasma concentration versus time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) increasing proportionately with doses from 25 to 261 mg/m^2. The peak concentration (theoretically end-of-infusion concentration) generally appeared to increase in

proportion with dose, although moderate to large interindividual variability (IIV) was apparent. MLN4924 plasma concentrations declined in a bi-exponential manner at the end of infusion, with little or no notable drug accumulation following once-daily dosing for 5 consecutive days or more intermittent dosing (ie, Days 1, 3, and 5; Days 1, 2, 8, and 9; Days 1, 8, and 15; Days 1 and 8; or Days 1, 4, 8, and 11). This is consistent with a mean terminal elimination half-life ($t_{1/2}$) of approximately 10 to 11 hours estimated across doses and schedules. Additionally, a preliminary population PK analysis indicated that MLN4924 systemic clearance (CL) (IIV in CL ~ 27% coefficient of variation [CV]) and volume of distribution (V_{ss}) (IIV central volume ~ 43% CV; IIV peripheral volume ~ 28% CV) appear to increase with increasing body size (body surface area [BSA] range 1.48-2.72 m^2) supporting BSA-normalized dosing in minimizing variability in exposure.

Additional information on the nonclinical and clinical PK of MLN4924 is provided in the IB.

1.4 MLN4924 Clinical Experience

Single-agent MLN4924 has been studied in 4 phase 1 clinical trials in patients with advanced nonhematologic malignancies (Study C15001); lymphoma and multiple myeloma (Study C15002); AML, MDS, or ALL (Study C15003); and melanoma (Study C15005). These were all single-agent, dose-escalation studies. Based on information available as of 02 April 2013, 227 patients were enrolled into these studies, and safety data are available and summarized for 224 of these patients (ie, those included in the Safety population).

MLN4924 was administered as a 1-hour IV infusion in these protocols. Six dosing schedules using a 21-day cycle were assessed across these studies (dosing on Days 1-5; Days 1, 3, and 5; Days 1 and 8; Days 1, 2, 8, and 9; Days 1, 8, and 15; and Days 1, 4, 8, and 11) in a coordinated fashion.

Study C15001 was conducted in 62 patients with solid tumors. The median age of the patients included in the Safety population was 59.5 years, with a range from 34 to 84 years. One patient (a 45-year-old man with metastatic melanoma and bone and lung involvement) had a partial response (PR) on Schedule A (Days 1-5) at a dose of 25 mg/m^2. In addition, 13 patients with the following solid tumors remained on treatment for at least 5 cycles, and all achieved a best response of stable disease (SD) that lasted for up to 9 cycles: colorectal carcinoma (6), melanoma (3), breast cancer (2), and small cell lung cancer (SCLC) and head and neck cancer (1 each) (C15001 Clinical Study Report [CSR]).

Study C15002 began in June 2008, and 56 patients with multiple myeloma (21) or lymphoma (35) were enrolled. The median age of the patients included in the Safety population was 60.0 years, with a range from 26 to 90 years. As of 30 September 2013, 3 PRs were observed in this study at doses of 110 to 196 mg/m^2: 1 patient each with diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma, and peripheral T-cell lymphoma. The patient with DLBCL achieved PR in Cycle 3, and the duration of this response was 134 days.

Study C15003 began in July 2009, and 72 patients were enrolled as of 28 October 2013 in this phase 1 study evaluating single-agent MLN4924 in several 21-day dosing schedules in patients with AML (patients with MDS and ALL were also evaluated in this study). For Schedule A (Days 1, 3, and 5), 4 dose levels were determined safe: 25, 33, 44, and 59 mg/m^2. The maximum tolerated dose (MTD) for Schedule A was established at 59 mg/m^2 based on a dose-limiting toxicity (DLT) of increased transaminases observed at a dose level of 78 mg/m^2. Dosing in Schedule B (Days 1, 4, 8, and 11) was de-escalated to 110 mg/m^2 based on 2 serious adverse events (SAEs) for patients dosed at 147 mg/m^2: 1 fatal (acute renal failure) and 1 life threatening (cardiac failure). The dose was subsequently reduced to 83 mg/m^2 to further enhance the safety margin. Schedule C (Days 1, 8, and 15) was tested in 2 patients (both received only 1 cycle of treatment), and Schedule D (Days 1, 4, 8, and 11 in combination with azacitidine) was tested in only 1 patient (although the patient received only MLN4924). Sixteen patients were enrolled in an additional expansion cohort, Schedule E, which was added to this protocol to further evaluate the dosing schedule of MLN4924 on Days 1, 3, and 5 at a fixed dose of 50 mg/m^2.

Both Schedules A and E (Days 1, 3, and 5) and Schedule B (Days 1, 4, 8, and 11) of MLN4924 administration appeared to be generally well tolerated. NEDD8-activating enzyme inhibition with MLN4924 demonstrated clinical activity in highly refractory/multiply relapsed AML patients. As an example, a 29-year-old woman with relapsed (French-American-British subtype M4) acute AML (with isolated trisomy 8) following allogeneic stem cell transplantation achieved complete remission after Cycle 1 treatment on Schedule A (Days 1, 3, and 5) with 25-mg/m^2 MLN4924. Her cytogenetic complete remission continued before she experienced extramedullary disease progression in Cycle 8. Prior treatments included “7 and 3” induction therapy followed by high-dose cytarabine and then allogeneic bone marrow transplantation.

Study C15005 was conducted in patients with melanoma. Thirty-seven patients were enrolled, and the median age of the patients in the Safety population was 61.8 years, ranging

from 33 to 79 years. Six patients stayed on the study for at least 6 cycles and achieved a best response of SD, and 1 patient achieved a PR (C15005 CSR).

In addition to single-agent studies, MLN4924 is currently being studied in combination with azacitidine in patients with AML. Study C15009 is a dose-escalation study that began in April 2013, and 15 patients 60 years of age or older with newly diagnosed AML have been enrolled as of 08 January 2014. The MTD of MLN4924 has been established at 20 mg/m^2 on Days 1, 3, and 5 in combination with azacitidine 75 mg/m^2 on Days 1 through 5, 8, and 9 in 28-day cycles. This study is ongoing.

Overall, the intermittent schedule of drug administration was better tolerated than the daily schedule. The identified risks of MLN4924 treatment are increased heart rate, diarrhea, nausea, vomiting, pyrexia, liver function test (LFT) abnormal, musculoskeletal pain, and myalgia (see Section 1.6.1; additional information is available in the Development Core Safety Information [DCSI]).

A comprehensive review of the clinical trial safety data has shown that toxicity involving multi-organ failure on Cycle 1, Day 1, including SAEs of renal, hepatic, and cardiac failure, some with a fatal outcome, has been observed in MLN4924 studies. Based on the observation that these events are associated with higher MLN4924 doses, the sponsor has determined that newly enrolling patients will receive MLN4924 at doses equal to or below 100 mg/m^2. Our current understanding of the renal toxicity observed with MLN4924 suggests that it is not a primary event; it is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response. Patients will be monitored closely for events of multi-organ failure after MLN4924 dosing.

In October 2012, a revised risk mitigation strategy including dose reduction was implemented across the MLN4924 program. As of January 2014, approximately 60 additional patients have been treated in single-agent and combination studies, and no Cycle 1, Day 1 SAEs have been observed. The majority of patients in these studies received MLN4924 at a dose of 50 mg/m^2 or lower.

Hepatotoxicity has been noted following administration of MLN4924 in patients with advanced malignancy, including elevations of liver transaminases, alkaline phosphatase (ALP), and bilirubin. Grade 1, 2, and 3 increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been observed in patients receiving the 50-mg/m^2 dose on Days 1, 3, and 5 in Schedule E of Study C15003. The patients experiencing these changes in laboratory values have been asymptomatic. This type of elevation in

transaminases had been observed previously in patients treated with MLN4924. The elevations in laboratory values have been reversible with dose modification including dose delay and reduction. Patients with elevated transaminases have been successfully rechallenged at lower doses.

Preliminary pharmacodynamic analyses in both hematologic and nonhematologic indications demonstrate target and downstream pathway inhibition following MLN4924 dosing at all doses tested in tumor and surrogate tissues. MLN4924-NEDD8 adduct is a unique molecular species formed as a consequence of the intracellular interaction of NAE with MLN4924 and NEDD8, and is indicative of MLN4924 inhibition of NAE.[(4)] MLN4924-NEDD8 adduct was detected by immunohistochemistry in postdose but not predose solid tumor biopsies in 11/11 patients demonstrating target inhibition 3 to 6 hours following MLN4924 dosing in all cases (dose range 50-83 mg/m^2). In addition, changes in CDL substrates Cdt-1 and Nrf2 were investigated in predose and postdose skin and tumor biopsies, with the majority of patients demonstrating postdose increases (1.5- to 25-fold) in Cdt-1 and/or Nrf2 in skin (27/34 patients) or tumor (9/11 patients). In addition, pharmacodynamic assessments of MLN4924 adduct and Cdt-1 in predose and postdose bone marrow aspirates obtained from patients with AML or high-grade MDS indicate target and pathway inhibition throughout the dose range tested (25-78 mg/m^2).

Additional information on safety and pharmacodynamics is provided in the IB.

The risks of MLN4924 treatment, based on preliminary findings from the clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, are presented in Section 1.6.1.

Antitumor Activity of MLN4924 in Solid Tumors

MLN4924 has been investigated as a single agent in solid tumors in 2 phase 1 studies: C15001 was conducted in patients with any solid tumors for whom prior therapies had failed, and Study C15005 was conducted in patients with melanoma that was relapsed/refractory to prior therapies. These studies were designed to determine safe and tolerable doses of MLN4924 in various solid tumors and establish a safety database for the molecule. The antitumor activity of MLN4924 as a single agent was also investigated in these studies. Overall, a total of 99 patients with various solid tumors have been treated in these 2 phase 1 studies.

In Study C15001, 13 patients with the following solid tumors stayed on the study for at least 5 cycles: colorectal carcinoma (6); melanoma (3); breast cancer (2); and SCLC and head and neck cancer (1 each).

Among 20 evaluable patients with melanoma in Study C15005, the disease control rate, defined as the proportion of patients achieving SD or better at first restaging, was 50% (10/20); 6 patients stayed on the study for at least 5 cycles. One 60-year-old woman with wild type-BRAF disease who progressed through multiple (> 6) prior therapies achieved a PR at Cycle 4. She was treated at the 209-mg/m^2 dose level of MLN4924.

The results of these studies indicate potential antitumor activity of MLN4924 in a variety of solid tumors in patients who have been heavily treated with multiple lines of prior therapy and who are typically very difficult to treat.

The use of combination therapy with standard of care (SoC) agents builds on nonclinical data demonstrating sensitivity to MLN4924 in certain types of malignancies such as colon cancer, non-small cell lung cancer (NSCLC), SCLC, melanoma, breast cancer, and esophageal cancer and its augmentation by standard chemotherapy agents (see Section 1.2); limited clinical data as described above; and the strength of published data with well-established chemotherapies used in various malignancies.

Study C15010, a dose-escalation study of MLN4924 in combination with SoC, is being conducted in patients with solid tumors for whom prior therapies have failed. As of 09 January 2014, 18 patients were treated with MLN4924 in combination with docetaxel, carboplatin, or carboplatin+paclitaxel. Based on preliminary data, these combinations have shown evidence of clinical benefit in the form of multiple PRs and extended durations of SD. The study is still in the dose-finding phase, and an MTD has not been established in any of these combinations. The current dose levels being investigated are:

- Docetaxel Arm: MLN4924 25 mg/m^2 on Days 1, 3, and 5 of a 21-day cycle in combination with docetaxel 75 mg/m^2 on Day 1.
- Carboplatin+Paclitaxel Arm: MLN4924 25 mg/m^2 on Days 1, 3, and 5 of a 21-day cycle in combination with carboplatin AUC5+paclitaxel 175 mg/m^2 on Day 1.

1.5 Study Rationale

1.5.1 Rationale for Drug-drug Interaction Assessment (Part A)

1.5.1.1 Study Rationale

Hepatic metabolism appears to be the major route of elimination for MLN4924. While no definitive information is currently available on the elimination pathways of MLN4924 in humans, urinary excretion of unchanged MLN4924 was found to be low (< 5%) in rats and primates. In vitro drug metabolism data indicate that MLN4924 is metabolized via hydroxylation and oxidation, predominantly by CYP3A4. The estimated contribution of CYP3A4 to MLN4924 biotransformation (97%) is largely above the 25% threshold of potential clinical relevance for drug-drug interactions (DDIs) based on United States (US) Food and Drug Administration (FDA) and European Medicines Agency guidance documents.[5, 6]

MLN4924 is in fact considered to be a sensitive CYP3A substrate as physiologically based PK modeling and simulation predict an 8- to12-fold increase in area under the plasma concentration versus time curve (AUC) when co-administered with the strong CYP3A4 inhibitor probe, ketoconazole. CYP3A is a major subclass of the CYP enzymes, accounting for more than 30% of total CYP proteins in the liver. Given the likelihood of a positive interaction between MLN4924 and a strong CYP3A inhibitor that may result in a clinically meaningful increase in MLN4924 exposure due to inhibition of CYP3A-mediated hepatic metabolism following IV administration, the impact of a less strong (or moderate) CYP3A inhibitor will also be evaluated. For drugs that distribute into red blood cells, the blood to plasma (B/P) ratio is important for estimation of in vivo hepatic metabolic clearance; however, the value is not always available. In vitro studies showed that MLN4924 partitioned extensively into erythrocytes with a B/P ratio that is concentration-dependent and saturable. Limited blood sampling will be performed in this study for in vivo determination of B/P ratio and to inform estimation of human blood clearance. Until the magnitude of such potential interactions is characterized in a clinical DDI study, co-administration of moderate and strong CYP3A inhibitors is not currently permitted in the ongoing clinical studies of MLN4924.

Fluconazole and itraconazole, 2 antifungal agents, are among choices of moderate and strong inhibitors of CYP3A4, respectively, that are recommended in regulatory guidelines.[5, 6] Fluconazole is an inhibitor of CYP3A4, CYP2C9, and CYP2C19 enzymes but not an inhibitor of transporters. Acute (400 mg) and steady-state (200 mg once daily

[QD]) administration of fluconazole has been shown to increase the AUC of orally administered midazolam up to 3.9-fold, which meets the criterion for a moderate CYP3A4 inhibitor.[7] There is no effect of food on the oral bioavailability of fluconazole tablets.[8] Itraconazole (200 mg QD), another validated inhibitor probe, was in fact chosen in place of ketoconazole based on recent FDA communications advising against its use for drug interaction studies due serious side effects (fda.gov/Drugs/DrugSafety/ucm371017.htm, FDA advises against using oral ketoconazole in drug interaction studies due to serious potential side effects, Accessed 13 January 2014).[9] Itraconazole is commercially available as an oral solution or as capsules.[10] Results from a cross-study comparison of solution and capsules indicated that when these 2 oral formulations are administered under optimal conditions for absorption, the bioavailability of the oral solution relative to the capsules is higher. Consequently, and in accordance with the FDA DDI Guidance for Industry, the oral solution of itraconazole administered on an empty stomach is selected for this study.[5] Use of these CYP3A4 inhibitor probes belonging to the class of azole antifungal agents in this study is most appropriate as they are relevant to the target (AML) patient population.

Results from this study will inform strategies for managing potential DDIs with moderate and strong CYP3A inhibitors in future clinical studies of MLN4924 and additionally contribute to the long-term clinical pharmacology objectives of the MLN4924 development program.

1.5.1.2 MLN4924 Dose Rationale for Part A

In phase 1 clinical studies, patients have been receiving MLN4924 administered IV at doses ranging from 25 to 278 mg/m^2 on multiple schedules for up to 19 cycles. Single-agent MLN4924 was specifically investigated in patients with solid tumors in 2 phase 1 studies: Study C15001 was conducted in patients with any solid tumors for whom prior therapies had failed, and Study C15005 was conducted in patients with melanoma that was relapsed/refractory to prior therapies. A total of 99 patients with various solid tumors have been treated in these studies designed to determine safe and tolerable doses of MLN4924.

In Study C15001, sequential cohorts of patients received MLN4924 as a 1-hour infusion on 4 different schedules. Of these schedules, the 2 in which MLN4924 was administered on Days 1, 3, and 5 on a 21-day cycle were generally better tolerated than those with once-daily dosing on 5 consecutive days at lower doses, or higher doses administered once weekly with a longer infusion. Common toxicities were diarrhea, nausea, vomiting, and increased LFTs.

After cross-program review, patients in ongoing and future studies will receive MLN4924 at doses equal to or below 100 mg/m^2.

The IV dose of MLN4924 (8 mg/m^2) selected for the study is approximately 14-fold lower than starting doses of MLN4924 equal to or above 110 mg/m^2, which were associated with an increased frequency of severe Cycle 1, Day 1 adverse events (AEs) in phase 1 studies of MLN4924. Only a single dose of MLN4924 will be administered in the presence of the CYP3A inhibitor. This low dose is anticipated to provide an adequate safety margin for conduct of this DDI assessment, based on the predicted 8- to 12-fold increase in MLN4924 systemic exposure (AUC) upon strong CYP3A inhibition by the inhibitor probe ketoconazole. The expectation is based on model-based simulations of DDI potential (SimCYP®) using in vitro data on relative contribution of CYP3A to overall metabolism, in vivo preclinical information on drug disposition, and clinical PK data available to date on MLN4924.

On the basis of emerging data from this study, the primary purpose of Amendment 1 is to further evaluate the effect of the strong CYP3A inhibitor itraconazole on MLN4924 PK at the clinically relevant dose of 20 mg/m^2. The information from this additional Itraconazole Arm will provide further understanding of the contribution of CYP3A metabolism to the disposition of MLN4924 in humans within the clinically relevant dose range in support of adequate labeling.

The proposed single IV dose of MLN4924, 20 mg/m^2, is approximately 5-fold lower than doses of MLN4924 equal to or above 110 mg/m^2, which were associated with more severe Cycle 1 Day 1 adverse events in phase 1 studies of MLN4924. Also, based on the dose-linear PK of MLN4924 and observed 23% increase in MLN4924 plasma systemic exposure by itraconazole at a single 8-mg/m^2 dose, it can be inferred that exposures of MLN4924 when administered at a single 20-mg/m^2 dose with itraconazole can be expected to be well below exposures seen at doses ≥ 110 mg/m^2. Conservatively, enrollment into the Itraconazole Arm, 20-mg/m^2 MLN4924 Cohort will begin once Part A PK and safety data from 3 PK-evaluable patients treated with 15-mg/m^2 MLN4924+itraconazole, as an intermediate safety lead-in step, have confirmed that the anticipated safety margin is adequate for the proposed evaluation of the drug interaction with itraconazole at the 20-mg/m^2 dose of MLN4924.

1.5.1.3 Rationale for Inclusion of Blood Pharmacodynamic Assessment

This study will also include assessment of blood-based pharmacodynamic markers. Investigations of pharmacodynamic biomarker modulation of NAE pathway inhibition were performed in both tumor and surrogate tissues in previous phase 1 studies of MLN4924. Changes in pharmacodynamic biomarkers following MLN4924 treatment as a single agent indicative of target and pathway inhibition were detected at all doses tested (25-278 mg/m^2). Therefore, the lower limit of target and pathway inhibition has not been determined to date. The use of a dose approximately one-third of the lowest dose tested to date in humans will enable further exploration of PK-pharmacodynamic relationships at systemic exposures of MLN4924 below those previously explored. CCI

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1.5.2 Rationale for Continued Treatment With MLN4924 in Combination With Standard of Care (Part B)

1.5.2.1 Study Rationale

After completing Part A, patients are given the opportunity to participate in Part B where they will receive combination treatment with MLN4924 and SoC chemotherapy.
Two chemotherapy regimens, docetaxel and carboplatin+paclitaxel, will be used in this study as combination partners with MLN4924. These regimens have been approved and are considered SoC therapies for various malignancies in front-line or relapsed/refractory settings.

Docetaxel is indicated as a single agent for locally advanced or metastatic breast cancer and for locally advanced or metastatic NSCLC after platinum therapy failure.

Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. In addition, paclitaxel in combination with cisplatin is indicated for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery or radiation therapy.

Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents (one established combination regimen consists of carboplatin and cyclophosphamide). Carboplatin is also indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.

Docetaxel, paclitaxel, and carboplatin are also approved in combination with other chemotherapeutic agents to treat other indications; refer to package inserts for additional information.

In addition to the approved indications outlined above, these agents are widely used in a variety of malignancies in patients for whom prior therapies have failed. Carboplatin/ paclitaxel is also widely used for treatment of newly diagnosed NSCLC.

For a detailed description of each of these medications, please see Section 6.11. The choice of the above chemotherapy agents in combination with MLN4924 in this study is based on the following considerations:

- These agents have been well recognized as SoC in a number of malignancies in front-line (carboplatin+paclitaxel) or in various relapse settings (both regimens).
- Their safety profiles, risks, and benefits have been widely studied and reported.
- Additive/synergistic effect of these agents in combination with MLN4924 has been studied in a number of in vitro and in vivo models in house.

Therefore, it is thought that the above SoCs will serve as reasonable partners in combination with MLN4924 for investigations in patients with various solid tumors in this study.

As discussed in Section 1.4, MLN4924 in combination with SoC is currently being investigated in Study C15010, a multi-arm, phase 1b, dose-escalation study of MLN4924 in combination with docetaxel or carboplatin+paclitaxel in patients with solid tumors for whom prior therapies have failed. This study is ongoing, and no MTD has been established yet. The current dose levels that are being investigated are:

- Docetaxel Arm: MLN4925 25 mg/m^2 on Days 1, 3, and 5 of a 21-day cycle in combination with docetaxel 75 mg/m^2 on Day 1

- Carboplatin+Paclitaxel Arm: MLN4924 25 mg/m^2 on Days 1, 3, and 5 of a 21-day cycle in combination with carboplatin AUC5+paclitaxel 175 mg/m^2 on Day 1

1.5.2.2 MLN4924 Dose Rationale in Combination With Standard of Care

Patients will receive MLN4924 in combination with either docetaxel or carboplatin+paclitaxel at a dose regimen informed from Study C15010 that has been deemed tolerable (eg, no DLTs in 3 patients or no more than 1 DLT in 6 patients). The selected dose may be adjusted accordingly based on information obtained from the ongoing review of safety data. The information learned from Study C15010, including the tolerable dose levels, will be provided to the sites in writing and per the Study Manual.

1.6 Potential Risks and Benefits

Given limited existing clinical experience, it is not known whether patients will benefit from participation in this study. However, a number of patients treated with MLN4924 as a single agent did demonstrate clinical benefit based primarily on prolonged SD (see Section 1.4). In addition, it is anticipated that the SoC therapies used in Part B of this study may provide additional clinical benefit to patients. Study C15010 is an open-label, dose-finding study to assess MLN4924+SoC and is ongoing. Eighteen patients have been treated with MLN4924 in combination with docetaxel, carboplatin, or carboplatin+paclitaxel. Based on preliminary data, these combinations have shown evidence of clinical benefit in the form of multiple PRs and extended durations of SD.

1.6.1 Risks of MLN4924 Therapy

Safety information gained from single-agent clinical studies of MLN4924 and from toxicology studies in rats and dogs has been used to guide the safety evaluation of MLN4924. Additional information on risks is provided in the IB and the DCSI.

Based on preliminary findings from the single-agent clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, the risks of MLN4924 treatment are presented below.

Identified Risks

- Increased heart rate
- Diarrhea
- Nausea
- Vomiting
- Pyrexia
- Liver function test abnormal
- Musculoskeletal pain/myalgia

Potential Risks

There are potential risks in the MLN4924 program that require further monitoring. While the potential toxicities listed below may be severe or life threatening, it is anticipated that they can be managed by clinical monitoring and intervention.

Potential Risks From Phase 1 Studies (at Higher Doses)

There are events that have been reported in phase 1 studies, which have been closed, including at doses and schedules substantially higher than those being used in current clinical trials. These events are being considered potential risks for the doses and schedules currently being studied:

- Multi-organ failure that could result in death
- Renal failure
    - The events of multi-organ failure (hepatic, renal, and cardiac) with a fatal outcome, and renal failure alone, have been reported at doses of MLN4924 ranging from 110 to 278 mg/m^2. Please refer to Section 1.4 for additional information about multi-organ failure and dosing.

- Cardiac arrhythmias
    - All events were supraventricular arrhythmias; all except 1 were unrelated. The case of atrial fibrillation assessed by the investigator as related occurred in a patient with cardiovascular risk factors.
- Myelosuppression with increased susceptibility to infection, bleeding, and anemia
- Acute phase response
- Gastrointestinal (GI) toxicity including or resulting in dehydration, and electrolyte imbalance
- Hypophosphatemia

Potential Risks Confounded by Underlying Disease or Malignancy

Events have been reported from clinical trials that are confounded by the patient's underlying medical condition, including malignancy. These events are noted in the absence of randomized, controlled data:

- Fatigue
- Chills
- Decreased appetite
- Neutropenia
- Febrile neutropenia
- GI bleeding
    - All events were assessed by the investigator as unrelated; the majority occurred in the setting of thrombocytopenia.

Potential Risks Primarily Based on Findings from Animal Studies

Potential risks that are derived from findings in animal studies in rats and dogs include:

- Cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure, and increased diastolic blood pressure.
- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.
- Effects on the testes and ovaries that represent a reproductive hazard, including sterility.
- Increased developmental risk to the fetus or embryo.
- Decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, and high). This finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses.
- Prolongation of the activated partial thromboplastin time (aPTT).
- Local tissue injury when administered SC.

Hepatotoxicity has been noted following administration of MLN4924 in patients with advanced malignancy, including elevations of liver transaminases, ALP, and bilirubin (see Section 1.4). Liver enzymes and liver function are frequently monitored during clinical studies of MLN4924. Acetaminophen and acetaminophen-containing compounds may not be used in Part A; however, they may be used judiciously in Part B and should not exceed a dose of 2 g of acetaminophen in a 24-hour period (see Section 6.5).

Patients must be carefully evaluated at screening and before each MLN4924 dose for early symptoms and signs of hemodynamic compromise or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Guidance on rehydration is provided in Section 6.8.

These potential toxicities will be managed by careful, frequent monitoring and intervention, as needed, with supportive care. It is possible that MLN4924 will have toxicities that were

not observed in or predicted from the studies completed in rats and dogs, or have not yet been identified in patients.

Patients will be monitored closely when they are receiving this agent and for at least 30 days after their last dose for these anticipated and potential toxicities and for unanticipated toxicities. Monitoring will include the following: laboratory assessments, physical examinations, SAE and AE reporting, and safety review (see Section 9.1).

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

1.6.2 Risks of Fluconazole Treatment

Anaphylaxis

In rare cases, anaphylaxis has been reported in patients who received fluconazole (brand name DIFLUCAN®). Patients have rarely developed exfoliative skin disorders during treatment with fluconazole. In patients with serious underlying diseases (predominantly acquired immunodeficiency syndrome and malignancy), these have rarely resulted in a fatal outcome.

Cardiac Dysrhythmias

> *Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. Most of these reports involved seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities, and concomitant medications that may have been contributory.*[8]

Hepatotoxicity Warning

> *DIFLUCAN should be administered with caution to patients with liver dysfunction. DIFLUCAN has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of DIFLUCAN-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex, or age of the patient has been observed. DIFLUCAN hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests*

during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to DIFLUCAN.[8]

For more details, refer to the fluconazole oral solution US Package Insert (USPI).[8]

Drug Interaction Precautions

See the DIFLUCAN USPI Sections on CLINICAL PHARMACOLOGY: Drug Interaction Studies and CONTRAINDICATIONS for additional information.

- Fluconazole is a potent inhibitor of CYP isoenzyme 2C9 and a moderate inhibitor of CYP3A4; therefore, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 co-administered with fluconazole (see Section 6.5).

Risks of MLN4924 and Fluconazole as Combination Therapy

Based on the known individual safety profiles of MLN4924 and fluconazole, the following potential risks of combination therapy may apply: headache, abdominal pain, nausea, diarrhea, and serum transaminase elevations.

1.6.3 Risks of Itraconazole Treatment

Congestive Heart Failure and Cardiac Effects

When itraconazole (SPORANOX®) was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen.

SPORANOX® (itraconazole) oral solution should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections.[10]

If signs or symptoms of congestive heart failure occur during administration of itraconazole oral solution, continued use should be reassessed.

Cardiac Dysrhythmias and Drug Interaction Warning

Co-administration of cisapride, oral midazolam, nisoldipine, felodipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), lovastatin,

> *simvastatin, ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) or methadone with SPORANOX® (itraconazole) Capsules or Oral Solution is contraindicated. SPORANOX®, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, methadone, levacetylmethadol (levomethadyl), or quinidine concomitantly with SPORANOX® and/or other CYP3A4 inhibitors.*

These medications are excluded from this study (see Section 6.5).

Other Cardiac Effects

Please see the SPORANOX® USPI WARNINGS section under the heading CARDIAC DISEASE for ischemic valvular disease, chronic obstructive pulmonary disease (COPD), renal and edematous disorders (including postmarketing reports of peripheral edema and pulmonary edema), and additional information on the negative inotropic effects of itraconazole when co-administered with calcium channel blockers.

Hepatotoxicity Warning

> *SPORANOX® has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Continued itraconazole oral solution use is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk.*[(10)]

For additional information on the safety profile of SPORANOX®, please refer to the USPI.[(10)]

Drug Interaction Precautions

Please consult the PRECAUTIONS/DRUG INTERACTIONS section of the SPORANOX® USPI for additional information.

Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. SPORANOX® may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with SPORANOX® (see Section 6.5).

Risks of MLN4924 and Itraconazole as Combination Therapy

Based on the known individual safety profiles of MLN4924 and itraconazole, the following potential risks of combination therapy may apply: fever, nausea, vomiting, diarrhea, and hepatotoxicity.

1.6.4 Risks of Docetaxel Treatment

Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

Severe hypersensitivity, including very rare, fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of docetaxel and administration of appropriate therapy.

Docetaxel is contraindicated if the patient has a history of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80.

Severe fluid retention may occur despite dexamethasone.

For more details, refer to the Taxotere® (docetaxel) USPI.[11]

1.6.4.1 Hepatotoxicity Warning

Docetaxel should not be given if total bilirubin is greater than the upper limit of the normal range (ULN) or if AST or ALT is greater than 1.5 times the ULN. Liver function test elevations increase the risk of severe or life threatening complications. Liver function tests should be obtained before each treatment cycle.

1.6.4.2 Hematologic Warning

Docetaxel should not be given if the absolute neutrophil count (ANC) is less than 1500 cells/mm^3.

1.6.4.3 Risks of MLN4924 and Docetaxel as Combination Therapy

Based on the known individual safety profiles of MLN4924 and docetaxel, the following potential risks of combination therapy may apply: death, hypersensitivity, hepatoxicity, neutropenia, and fluid retention (cardiac/pulmonary). With regard to docetaxel, treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

1.6.5 Risks of Carboplatin and Paclitaxel Therapy

See Section 15.1 for information on the hematologic toxicity of carboplatin alone and in combination with paclitaxel.

1.6.5.1 Carboplatin

Anaphylaxis-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

Vomiting is another frequent drug-related side effect.

Carboplatin Injection is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds.

Carboplatin Injection should not be employed in patients with severe bone marrow depression or significant bleeding.

For more details, please refer to the Paraplatin® (carboplatin) USPI.[(12)]

Nephrotoxicity Warning

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

Hematologic Warning

Bone marrow suppression is dose related and may be severe, resulting in infection or bleeding. Peripheral blood counts should be frequently monitored during carboplatin treatment and, when appropriate, until recovery is achieved.

Anemia may be cumulative and may require transfusion support.

1.6.5.2 Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Severe conduction abnormalities have been documented in less than 1% of patients during paclitaxel therapy and, in some cases, require pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered, and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Paclitaxel is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

For more details, please refer to the Taxol® (paclitaxel) USPI.[13]

Hematologic Warning

Paclitaxel Injection, US Pharmacopeia (USP) therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3. To monitor for the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel Injection, USP.

1.6.5.3 Risks of MLN4924 and Carboplatin+Paclitaxel as Combination Therapy

Based on the known individual safety profiles of MLN4924 and carboplatin+paclitaxel, the following potential risks of combination therapy may apply: bone marrow suppression, hypersensitivity/anaphylaxis reactions, and hepatotoxicity. Renal effects of nephrotoxic compounds (see Section 15.2) may be potentiated by carboplatin.

1.6.6 Summary of Risks of Fluconazole, Itraconazole, or Standard of Care Therapies in Combination With MLN4924

Potential overlapping toxicities of CYP3A-mediated inhibitors and SoCs in combination with MLN4924 that are described in more detail above are summarized in Table 1-1.

Table 1-1 Potential Overlapping Toxicities With MLN4924 in Combination With Fluconazole, Itraconazole, or Standard of Care Therapies

Agent	Potential Overlapping Toxicities With MLN4924
Fluconazole	Abdominal pain Nausea Diarrhea Hepatotoxicity Headache
Itraconazole	Fever Nausea Vomiting Diarrhea Hepatoxicity Cardiac dysrhythmias (with concomitant CYP3A4 inhibitors)
Docetaxel	Death[a] Hypersensitivity Hepatoxicity Neutropenia Fluid retention (cardiac/pulmonary)
Carboplatin+paclitaxel	Bone marrow suppression Hypersensitivity/anaphylaxis reactions Hepatotoxicity Renal effects of nephrotoxic compounds may be potentiated by carboplatin

Abbreviations: CYP=cytochrome P450.

a Docetaxel treatment-related mortality increases with abnormal liver function, occurs at higher doses, and in patients with nonsmall cell lung cancer who received prior platinum-based therapy and are receiving docetaxel at 100 mg/m^2.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the effect of multiple-dose administration of fluconazole, a moderate CYP3A inhibitor, on the single-dose IV PK of MLN4924

- To assess the effect of multiple-dose administration of itraconazole, a strong CYP3A inhibitor, on the single-dose IV PK of MLN4924

2.2 Secondary Objectives

The secondary objectives for Part A are:

- To further evaluate the safety and tolerability of MLN4924

- To further describe the IV PK of MLN4924 before and after multiple oral dosing with fluconazole or itraconazole

The secondary objectives for Part B are:

- To further assess the safety and tolerability of MLN4924 in combination with docetaxel in patients with solid tumors
- To further assess the safety and tolerability of MLN4924 in combination with carboplatin and paclitaxel in patients with solid tumors
- To further evaluate disease response that may be observed with the combination of MLN4924 and docetaxel
- To further evaluate disease response that may be observed with the combination of MLN4924, carboplatin, and paclitaxel

2.3 Exploratory Objective

The exploratory objective for Part A is:

CCI

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoints

- Ratio of geometric mean, C_{max}, AUC from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-}tlast}$), and AUC from time zero to infinity ($AUC_{0\text{-}inf}$) of MLN4924 administered with fluconazole versus MLN4924 administered alone and 90% confidence intervals (CIs)
- Ratio of geometric mean, C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}inf}$ of MLN4924 administered with itraconazole versus MLN4924 administered alone and 90% CI

3.2 Secondary Endpoints

The secondary endpoints for Part A are:

- Adverse events, SAEs, assessments of clinical and laboratory values, weight, and vital sign measurements
- Pharmacokinetic parameters including but not limited to CL, first time to achieve maximum observed plasma concentration (T_{max}), V_{ss}, $t_{1/2}$, and B/P ratio of MLN4924

The secondary endpoints for Part B are:

- Adverse events, SAEs, assessments of clinical and laboratory values, weight, and vital sign measurements
- Measures of disease response including objective response rate and duration of response based on investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1)[(14)]

3.3 Exploratory Endpoints

The exploratory endpoint for Part A is:

CCI

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This study is an open-label, multicenter, parallel group, 2-arm, phase 1 study of MLN4924 designed to assess DDIs with the moderate and strong CYP3A inhibitors fluconazole and itraconazole, respectively. The patient population will consist of patients 18 years of age or older who have a histologically or cytologically confirmed metastatic or locally advanced solid tumor that is deemed appropriate for treatment with 1 of the 2 combination therapies in Part B of this study, or who have progressed despite standard therapy, or for whom conventional therapy is not considered effective.

It is expected that approximately 52 patients will be enrolled in this study to reach the intended total number of PK-evaluable patients in each arm/cohort. In the Fluconazole Arm, approximately 12 PK-evaluable patients will be enrolled. In the Itraconazole Arm, approximately 12 PK-evaluable patients will be enrolled in the 8-mg/m^2 and 20-mg/m^2 MLN4924 cohorts, and 3 additional PK-evaluable patients will be needed in the safety lead-in cohort. Once enrolled into the study, patients will begin treatment in Part A of the study. In Part A, patients will be administered MLN4924 via a 1-hour (± 5 minutes) IV infusion in combination with either fluconazole or itraconazole as indicated below. Once patients complete Part A (including the washout period), they can begin treatment in Part B of the study. In Part B, patients will be administered MLN4924 via a 1-hour (± 10 minutes as of Amendment 2) IV infusion in combination with either docetaxel or carboplatin+paclitaxel.

Part A: Drug-Drug Interaction Assessment

MLN4924+Fluconazole: Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This low dose of MLN4924 is anticipated to provide an adequate safety margin for DDI assessment (see Section 1.5.1.2). Patients will receive concomitant oral fluconazole at a starting dose of 400 mg on Day 4 and then 200 mg QD on Days 5 through 10. Pharmacokinetic samples will be taken after the MLN4924 dose on Day 1 and after the Day 8 dose of MLN4924 with fluconazole at predetermined time points (up to 72 hours after dosing) to assess the effect of fluconazole on the PK of MLN4924. Additional samples for determination of MLN4924 concentrations in whole blood will be collected on Day 1 only.

MLN4924+Itraconazole: Patients will receive a single dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8 (see dose cohorts below). Patients will receive concomitant oral itraconazole at a dose of 200 mg QD on Days 4 through 10. Pharmacokinetic samples will be taken after the MLN4924 dose on Day 1 and after the Day 8 dose of MLN4924 with itraconazole at predetermined time points (up to 72 hours after dosing) to assess the effect of itraconazole on the PK of MLN4924. Additional samples for determination of MLN4924 concentrations in whole blood will be collected on Day 1 only. The following dose cohorts will be enrolled sequentially within the Itraconazole Arm:

- Itraconazole Arm, 8-mg/m^2 MLN4924 Cohort: Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1

and Day 8. This low dose of MLN4924 is anticipated to provide an adequate safety margin for DDI assessment.

- Itraconazole Arm, Safety Lead-in 15-mg/m^2 MLN4924 Cohort: Patients will receive a single 15-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This safety lead-in cohort will confirm the safety margin is adequate before any patients are enrolled in the 20-mg/m^2 MLN4924 Cohort.

- Itraconazole Arm, 20-mg/m^2 MLN4924 Cohort: Patients will receive a single 20-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. This dose of MLN4924 falls within the clinically relevant dose range currently evaluated in Phase 1b combination studies of MLN4924 plus standard of care.

A preliminary PK analysis will be conducted after the first 4 to 8 patients have completed the Fluconazole Arm of Part A. After review of the emerging data from the Fluconazole Arm, patient assignment to the Itraconazole Arm will be initiated. Dose modifications of MLN4924 in the Itraconazole Arm may be reconsidered based on the magnitude of the interaction with the moderate CYP3A inhibitor fluconazole and the ability to accurately estimate PK parameters for DDI evaluation.

Following completion of the first 3 patients in the Itraconazole Arm, 8-mg/m^2 MLN4924 Cohort, preliminary PK data will be reviewed to guide expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients. If these emerging preliminary PK data indicate that the magnitude of the interaction with the strong CYP3A inhibitor itraconazole reaches the anticipated approximately 10-fold change, and individual drug exposures do not exceed those seen at doses of MLN4924 ≥ 110 mg/m^2, then up to 3 additional patients to provide 4 to 6 PK-evaluable patients will be enrolled. If the magnitude of the interaction with the strong CYP3A inhibitor itraconazole is much greater than anticipated (greater than the predefined safety margin of 14-fold), with individual MLN4924 exposures exceeding those seen at doses of MLN4924 ≥ 110 mg/m^2, then no additional patients will be enrolled in the Itraconazole Arm of Part A.

As of the implementation of Amendment 1, following completion of Part A by 3 PK-evaluable patients in the Safety Lead-in 15-mg/m^2 MLN4924 Cohort, safety and PK data will be reviewed to inform expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients in the 20-mg/m^2 MLN4924 Cohort. If the preliminary

PK data from the safety lead-in cohort indicate that the magnitude of the interaction between the proposed 20-mg/m^2 MLN4924 dose and the strong CYP3A inhibitor itraconazole would be greater than the predefined safety margin (5-fold, with individual MLN4924 exposures potentially exceeding those seen at doses of MLN4924 ≥ 110 mg/m^2), then no patients will be enrolled in the 20-mg/m^2 MLN4924 Cohort. Dosing with intermediate doses of MLN4924 and/or evaluation of the drug interaction with the moderate CYP3A inhibitor, fluconazole, may then be reconsidered if it is deemed necessary to further enhance our understanding of the effect of CYP3A inhibition on the PK of MLN4924.

Patients will be required to visit the clinic on Day 4 for their first dose of fluconazole or itraconazole. For both the Fluconazole and Itraconazole Arms, all doses of fluconazole and itraconazole will be administered on an empty stomach with the patient fasting from food and fluids, except water and prescribed medications, for 2 hours before and 1 hour after each dose. Patients are encouraged to take fluconazole or itraconazole doses at approximately the same time each morning and approximately 24 hours apart. On Day 8, patients will take fluconazole or itraconazole together with MLN4924 in the morning at the clinic.

In addition to blood sampling for PK, blood samples in the 24-hour postdose window of each arm following dosing on Day 1 and Day 8 will be collected to measure pharmacodynamic effects of MLN4924. These data will be pooled with data from other MLN4924 clinical studies to contribute to an integrated PK-pharmacodynamic analysis across the program.

Part B: Continued Treatment With MLN4924 in Combination With Standard of Care

After patients complete Part A, they will have the opportunity to continue in the study by participating in Part B. In Part B, patients will receive MLN4924 in combination with either docetaxel or carboplatin+paclitaxel at a dose regimen informed from Study C15010 that has been deemed tolerable (eg, no DLTs in 3 patients or no more than 1 DLT in 6 patients). The selected dose of MLN4924 may be adjusted based on information obtained from the ongoing review of safety data. Safety and disease assessments will be conducted in Part B of the study.

Study drug will be discontinued if a patient experiences study drug-related toxicities. Patients may discontinue therapy at any time. After completion of at least 12 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient

eligibility for continued treatment (Section 6.4.2) upon return from a treatment break, before treatment. Patients will attend the End-of-Study (EOS) visit 30 days after receiving their last dose of study drug.

Throughout the study, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained and assessed.

Computed tomography (CT) scans with IV contrast of the chest, abdomen, and pelvis will be performed as entry criteria for Part B (after completing of Part A). In addition, in Part B, CT scans with IV contrast encompassing the known sites of disease will be performed at every other cycle (Cycles 1 through 12), or after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 2), and at the EOS visit. Additional CT scans may be performed, per investigator's discretion, if clinically indicated. If CT scan does not provide adequate imaging, magnetic resonance imaging (MRI) may be used to evaluate sites of disease. Tumor response will be assessed by the investigator at these times using the RECIST criteria, version 1.1.[14]

4.2 Number of Patients

Approximately 52 patients will be enrolled in this study from approximately 3 study centers in the US, to reach the intended total number of PK-evaluable patients in each arm/cohort. Patients are considered to be enrolled when they receive their first dose of any drug. Patients who are not PK evaluable (see Section 8.1.4) will be replaced.

4.3 Duration of Study

Patients participating in Part B will be treated (after at least a 2-week [and up to 8-week] washout period after receiving their last dose of fluconazole or itraconazole in Part A) until they experience symptomatic deterioration or progressive disease (PD) (see definition in Section 15.3), or until their treatment is discontinued for another reason (see Section 7.6), or until the study is stopped. After completion of at least 12 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued treatment (Section 6.4.2) upon return from a treatment break, before treatment. The analyses for the CSR will be conducted after all patients enrolled in the study have provided PK assessments in Part A to meet the primary (DDI) objectives of the protocol or have

discontinued treatment. Patients still on therapy at this point will continue in the study through their EOS visit.

5. STUDY POPULATION

Confirmation of eligibility must be obtained before the patient can enter the study. After completion of Part A, patients who are to continue into Part B must meet the entry criteria listed in Section 7.4.20.

5.1 Inclusion Criteria

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

1. Male or female patients 18 years of age or older.

2. Patients must have a histologically or cytologically confirmed metastatic or locally advanced and incurable solid tumor that is deemed appropriate for treatment with 1 of the 2 chemotherapy regimens in Part B of this study, or have progressed despite standard therapy, or for whom conventional therapy is not considered effective. The tumor must be radiographically or clinically evaluable or measurable.

3. Recovered (ie, ≤ Grade 1 toxicity) from the effects of prior antineoplastic therapy.

4. Suitable venous access for the study-required blood sampling for MLN4924 PK and pharmacodynamic assessments.

5. Eastern Cooperative Oncology Group PS of 0 or 1 (refer to Section 15.4).

6. Clinical laboratory values as specified below within 3 days before the first dose of study drug:

   - Hemoglobin ≥ 9 g/dL
   - Absolute neutrophil count ≥ 1,500/mm^3 (refer to Section 15.5), not supported by growth factor
   - Platelet count ≥ 100,000/mm^3
   - Total bilirubin ≤ ULN
   - Prothrombin time (PT) and aPTT ≤ 1.5 × ULN

- Alanine aminotransferase, AST, and ALP $\leq 2.5 \times$ ULN
    - For patients to be treated with MLN4924+docetaxel in Part B, AST and ALT must be $\leq 1.5 \times$ ULN, and total bilirubin should be within the normal range.
- Serum creatinine ≤ 1.2 mg/dL or calculated/measured creatinine clearance ≥ 50 mL/minute (see Section 15.6)

7. Female patients who:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- As of Amendment 2, if they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Section 15.10), at the same time, from the time of signing the informed consent form (ICF) through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only [as of Amendment 2], and lactational amenorrhea [as of Amendment 2] 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 effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods for the female partner], withdrawal, spermicides only [as of Amendment 2], and lactational amenorrhea [as of Amendment 2] are not acceptable methods of contraception. Female and male condoms should not be used together.)

8. 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.

9. Patients who are willing to refrain from donating blood for at least 90 days after their final dose of MLN4924 and (for male patients) willing to refrain from donating semen for at least 4 months after their final dose of MLN4924.

5.2 Exclusion Criteria

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

1. Prior treatment with MLN4924; however, prior treatment with docetaxel, paclitaxel, and carboplatin is allowed.

2. Treatment with any systemic antineoplastic therapy or investigational products within 21 days before the first dose of study treatment.

3. Radiotherapy within 14 days before the first dose of study treatment.

4. Prior treatment with radiation therapy involving ≥ 25% of the hematopoietically active bone marrow.

5. Known hypersensitivity or history of severe intolerance or toxicity to study-assigned chemotherapy.

   Note: History of severe hypersensitivity reactions to docetaxel (polysorbate 80-based formulations) for patients to be treated with MLN4924+docetaxel; history of hypersensitivity to carboplatin for patients to be treated with MLN4924+carboplatin+paclitaxel; or history of severe hypersensitivity to paclitaxel (Cremophor-based formulations) for patients to be treated with MLN4924+carboplatin+paclitaxel in Part B

6. Known hypersensitivity/allergy to fluconazole or itraconazole or their respective excipients.

7. Systemic treatment with moderate and strong CYP3A inhibitors or inducers must be discontinued at least 14 days before the first dose of MLN4924. Moderate and strong CYP3A inhibitors and clinically significant CYP3A inducers were not permitted during Part A of the study or during Part B of the study until implementation of

Amendment 2; following implementation of Amendment 2 and completion of at least 12 cycles of treatment, concomitant use of moderate and strong CYP3A inhibitors is permitted in Part B (see Table 6-2 and Section 15.7). Patients must have no history of amiodarone use in the 6 months before the first dose of MLN4924.

8. Any life-threatening or serious medical or psychiatric illness unrelated to cancer that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

9. Major surgery within 14 days before the first dose of study treatment.

10. Active uncontrolled infection or severe infectious disease, such as pneumonia, meningitis, septicemia, or methicillin-resistant *Staphylococcus aureus* infection.

11. Clinically significant central nervous system disease defined as untreated, progressive, or requiring steroids for control of symptoms.

12. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of fluconazole or itraconazole including difficulty swallowing capsules.

13. Persistent diarrhea (≥ Grade 2) lasting > 3 days within 2 weeks before the first dose of study treatment.

14. Known hepatic cirrhosis, hepatitis B surface antigen-positive status, or suspected active hepatitis C infection.

    Note: Patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.

15. Known human immunodeficiency virus (HIV) positive status.

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

17. Uncontrolled high blood pressure (ie, systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg).

18. Left ventricular ejection fraction < 50% as assessed by echocardiogram or radionuclide angiography.

19. Congestive heart failure New York Heart Association Class III or IV, or Class II with a recent decompensation requiring hospitalization within 4 weeks before screening (Section 15.7).

20. Cardiomyopathy or history of ischemic heart disease.

    - Patients with ischemic heart disease who have had acute coronary syndrome (ACS), myocardial infarction (MI), or revascularization (eg, coronary artery bypass graft, stent) in the past 6 months are excluded. However, patients with ischemic heart disease who have had ACS, MI, or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll.

21. Arrhythmia (eg, history of polymorphic ventricular fibrillation or torsade de pointes). However, patients with < Grade 3 atrial fibrillation for a period of at least 6 months may enroll. Grade 3 atrial fibrillation is defined as symptomatic and incompletely controlled medically, or controlled with device (eg, pacemaker) or ablation, and is excluded. Patients with paroxysmal atrial fibrillation are permitted to enroll.

22. Prolonged rate corrected QT interval (QTc) ≥ 500 msec, calculated according to institutional guidelines.

23. Implantable cardioverter defibrillator.

24. Patients with a cardiac pacer whose heart rate is set at a fixed rate and patients on concomitant medication that may limit increase in heart rate in response to hypotension (eg, high-dose beta blocker).

25. Moderate to severe aortic or mitral stenosis or other valvulopathy (ongoing).

26. Known moderate to severe COPD (Section 15.9), interstitial lung disease, pulmonary fibrosis, and pulmonary arterial hypotension.

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).

6.1.1 MLN4924 and Fluconazole or Itraconazole Administration (Part A)

Patients will receive a single dose of MLN4924 given as an IV infusion on Day 1 and Day 8. Patients will receive either concomitant oral fluconazole or itraconazole on Days 4 through 10.

MLN4924+Fluconazole

Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. Patients will receive concomitant oral fluconazole at a starting dose of 400 mg on Day 4 and then 200 mg QD on Days 5 through 10.

MLN4924, 8 mg/m^2+Itraconazole

Patients will receive a single 8-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. Patients will receive concomitant oral itraconazole at a dose of 200 mg QD on Days 4 through 10.

MLN4924, 15 mg/m^2+Itraconazole (Safety Lead-in Cohort added per Amendment 1)

Patients will receive a single 15-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. Patients will receive concomitant oral itraconazole at a dose of 200 mg QD on Days 4 through 10.

MLN4924, 20 mg/m^2+Itraconazole (added per Amendment 1)

Patients will receive a single 20-mg/m^2 dose of MLN4924 given as a 1-hour (± 5 minutes) IV infusion on Day 1 and Day 8. Patients will receive concomitant oral itraconazole at a dose of 200 mg QD on Days 4 through 10.

Patients will receive MLN4924 diluted with 5% dextrose in a 250-mL bag via a 1-hour (± 5 minutes) IV infusion. MLN4924 should be administered through central or peripheral venous access.

The entire content of the MLN4924 IV bag will be infused at a constant rate over 1 hour (± 5 minutes). The start and end time of the IV infusion should be recorded accurately. To ensure that all the MLN4924 is administered, the infusion line will be flushed with saline or 5% dextrose immediately after administration or per similar institutional standards. The volume used for line flushing is not considered part of the volume of the MLN4924 IV bag to be documented. All infusion times must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours.

In Part B (see Section 6.1.2), the infusion may be slowed or stopped and restarted for any associated infusion-related reactions; however, this should be avoided in Part A. **If during Part A there is a need to interrupt or slow the IV infusion, contact the project clinician or designee as soon as possible for consideration of patient replacement as appropriate.** If the IV infusion is interrupted, 2 additional PK samples (1 sample drawn when the infusion is stopped and 1 sample drawn when the infusion is restarted) should be collected so that the patient may be considered evaluable. The exact date and time of each additional sample collection and the actual start and stop times of the infusion should be recorded accurately.

During Part A, all doses must be taken as outlined in the Schedules of Events. No doses should be missed or delayed due to patient scheduling. For both the Fluconazole and Itraconazole Arms, **all doses of fluconazole and itraconazole will be administered on an empty stomach with the patient fasting from food and fluids, except water and prescribed medications, for 2 hours before and 1 hour after each dose.** Patients will be required to visit the clinic on the morning of Day 4 for their first oral dose of fluconazole or itraconazole. On Days 5 through 7, patients will take their second, third, and fourth oral dose of fluconazole or itraconazole at home. While at home, patients are encouraged to take fluconazole or itraconazole oral doses at approximately the same time each morning and approximately 24 hours apart. On Day 8, patients will be instructed to come to the clinic in the morning without taking their morning dose of fluconazole or itraconazole; patients will be administered oral fluconazole or itraconazole first, followed by the 1-hour (± 5 minutes) IV infusion of MLN4924 approximately 20 minutes (± 10 minutes) after ingestion of the fluconazole tablet or itraconazole oral solution. On the morning of Days 9 and 10, patients will be asked to return to the clinic without taking their morning dose of fluconazole or itraconazole for PK, pharmacodynamic, and safety follow-up assessments.

If a patient fails to take the fluconazole or itraconazole dose within the time frame specified (ie, within ± 2 hours of first dosing time), that dose should be omitted and considered a missed dose. Patients should record any missed doses in their dosing diaries (see the Study Manual). If emesis occurs after study medication (fluconazole) ingestion, and if whole tablet(s) are visible in the vomitus, replacement tablet(s) should be taken; otherwise, the dose will not be re-administered, and the patient should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. In the event of emesis occurring after dosing with the itraconazole solution, the patient should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diaries (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses. In the case of missed dose or emesis for either fluconazole or itraconazole during Part A, patients may be considered unevaluable and may be replaced to ensure an adequate number of PK-evaluable patients. A patient who is considered unevaluable during Part A will have the opportunity to participate in Part B of the study.

6.1.2 Continued Treatment With MLN4924 in Combination With Standard of Care (Part B)

MLN4924 Administration

Patients will receive MLN4924 given as a 1-hour (±10 minutes as of Amendment 2) IV infusion in combination with either docetaxel or with carboplatin+paclitaxel at a dose regimen informed from Study C15010 that has been deemed tolerable (eg, no DLTs in 3 patients or no more than 1 DLT in 6 patients). The selected dose may be adjusted based on information obtained from the ongoing review of safety data. In Part B, the infusion may be slowed or stopped and restarted for any associated infusion-related reactions; however, this should be avoided in Part A.

In Part B only, Day 1 dosing may be delayed by up to 2 days (Cycles 1 through 12) or up to 2 weeks (after completion of Cycle 12; up to 4 weeks after consulting with the sponsor) to accommodate inclement weather, holidays, vacations, or other administrative reasons. See Section 7.4 for information about corresponding study procedures if dosing is delayed for reasons noted above. After completion of at least 12 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued

treatment (Section 6.4.2) upon return from a treatment break, before treatment. Refer to the Study Manual for additional instructions regarding study drug administration.

Docetaxel Administration

Docetaxel will be administered per institutional guidelines as a 1-hour IV infusion at a dose of 75 mg/m^2 on Day 1 combined with the recommended IV dose of MLN4924 on Days 1, 3, and 5. Refer to the most recent prescribing information for further details regarding docetaxel administration.[11]

Premedication for Docetaxel-Associated Hypersensitivity or Other Acute Reactions Guidelines

Premedication to prevent docetaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with dexamethasone (Decadron, 4 mg twice daily for 3 days), which should start 24 hours before docetaxel administration.

Carboplatin Administration

Carboplatin will be administered per institutional guidelines as a 30-minute IV infusion at a dose of AUC5 on Day 1 combined with the recommended IV dose of MLN4924 on Days 1, 3, and 5. Refer to the most recent prescribing information for further details regarding carboplatin administration.[12]

> *If a patient's glomerular filtration rate (GFR) is estimated based on serum creatinine measurements by the standardized Isotope Dilution Mass Spectrometry method, FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as:*
>
> *Total Carboplatin Dose (mg)=(target AUC) × (GFR+25) [Calvert formula]*
>
> *Maximum Carboplatin Dose (mg)=target AUC (mg × min/mL) × (150 mL/min)*
>
> *The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.*

For a target AUC=5, the maximum dose is 5 × 150=750 mg

For a target AUC=4, the maximum dose is 4 × 150=600 mg

Source: fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm, Carboplatin dosing, Accessed 19 February 2013.

Paclitaxel Administration

Paclitaxel will be administered per institutional guidelines as a 3-hour IV infusion at a dose of 175 mg/m^2 on Day 1 combined with the recommended IV dose of MLN4924 on Days 1, 3, and 5. Refer to the most recent prescribing information for further details regarding paclitaxel administration.[13]

Premedication for Paclitaxel-Associated Hypersensitivity or Other Acute Reactions

Premedication to prevent paclitaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with either dexamethasone (10 mg) 24 hours before and on the day of paclitaxel dosing or methylprednisone (solu-Medrol) immediately before paclitaxel dosing.

6.2 Reference/Control Therapy

No reference or placebo treatment will be used in this study. All eligible patients will receive treatment with MLN4924 in the absence or presence of fluconazole or itraconazole in Part A. Participation in Part B of the study is optional.

6.3 Definitions of Dose-Limiting Toxicity Equivalents (Part B)

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective 14 June 2010.[15] These criteria are provided in the Study Manual. Although this is not a dose escalation study, DLT equivalents will be collected. Dose-limiting toxicity equivalents will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with MLN4924, docetaxel, or carboplatin+paclitaxel. When a dose modification is warranted for safety, and the toxicity is thought to be attributable to the chemotherapeutic agent(s), consider dose reductions for chemotherapy first, if appropriate. Dose modification of MLN4924 may also be considered for events judged by the investigator to be directly related to MLN4924 (see Section 6.4.2) or chemotherapy-related toxicities that may have been exacerbated by MLN4924 in a combination setting.

Hematologic Dose-Limiting Toxicity Equivalents

- Any Grade 4 hematologic toxicity using NCI CTCAE, Version 4.03, with the exception of Grade 4 neutropenia lasting < 7 days in duration
- Grade 3 or greater neutropenia with fever > 38.5°C sustained for longer than 1 hour
- For patients in Part B, a delay in the initiation of Cycle 2 by ≥ 4 weeks due to a lack of adequate recovery from treatment-related toxicity (recovery to Grade ≤ 1 or to the patient's baseline values or to a level considered acceptable by the investigator after discussion with the project clinician or designee) due to hematologic toxicity believed not related to tumor infiltration (bone marrow evaluation may be required)

Nonhematologic Dose-Limiting Toxicity Equivalents

- Grade 3 or greater diarrhea that is uncontrolled despite maximal supportive therapy.
- Grade 3 or greater nausea or emesis that is uncontrolled despite the use of optimal antiemetic prophylaxis. Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a corticosteroid given in standard doses and according to standard schedules.
- Grade 3 or greater arthralgia/myalgia lasting longer than 48 hours that is uncontrolled despite the use of optimal analgesia.
- Grade 3 or greater electrolyte disturbance that is uncontrolled despite appropriate medical management.
- Any other Grade 3 or greater nonhematologic toxicity with the following exceptions:
    - Brief (< 1 week) fatigue
    - Hypophosphatemia that can be controlled with appropriate medical management
- For patients in Part B, a delay in the initiation of Cycle 2 of more than 2 weeks due to a lack of adequate recovery from nonhematologic toxicity (recovery to Grade ≤ 1 or to patient's baseline values or to a level considered acceptable by the investigator after discussion with the project clinician or designee).

- Other study drug-related, nonhematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a dose modification or discontinuation of therapy with MLN4924 (see Section 6.4.2).

Other Dose-Limiting Toxicity Equivalents

In addition, the following will be considered DLT equivalents if they occur within the first cycle:

- Any AE at least possibly related to the study drugs, regardless of NCI CTCAE grade, leading to dose modification of MLN4924 or other study treatments (docetaxel, carboplatin, or paclitaxel) in the next cycle.

- Patients will be monitored through all cycles of therapy for treatment-related toxicities.

6.4 Dose Modification Guidelines (Dose Delays, Dose Reductions, and Dose Interruptions) (Part B)

6.4.1 Dose Modification Guidelines for Specific Toxicities

The following apply to DLT equivalents occurring during any cycle of Part B of the study. For individual patients experiencing a DLT equivalent, treatment for each new cycle will be delayed until toxicity is reduced to ≤ Grade 1 or patient's baseline or to a level considered acceptable by the investigator after discussion with the project clinician or designee.

- Alopecia of any duration will not lead to dose modification or treatment delay.

- Patients receiving MLN4924+docetaxel may have a maximum of 2 dose modifications (if applicable) of chemotherapy agents as outlined below or modification of MLN4924 (see Section 6.4.2). Patients who require more than 2 dose modifications will be discontinued from the study.

- Patients receiving MLN4924+carboplatin+paclitaxel may have no more than 1 dose modification (if applicable) of chemotherapy agents as outlined below or modification of MLN4924 (see Section 6.4.2). Patients who require additional dose modifications will be discontinued from the study.

    - Paclitaxel is initially dosed at 175 mg/m^2. One dose reduction to 135 mg/m^2 may be considered.

  - Docetaxel is initially dosed at 75 mg/m^2. Up to 2 dose modifications to 60 and 45 mg/m^2 may be considered.

  - Carboplatin is initially dosed at AUC5. One dose reduction to AUC4 may be considered.

- In the event of a DLT equivalent, hold treatment and provide supportive care until the patient recovers to Grade 1 toxicity or baseline level before considering a dose modification as specified above. Patients with unresolved toxicities > Grade 1 lasting 3 weeks or longer from the date of the next scheduled treatment will be discontinued from the study.

- The decision to treat at a reduced dose level of SoC therapy is at the discretion of the investigator. Discussions with the project clinician or designee are encouraged.

Table 6-1 outlines the dose modification guidelines for specific toxicities.

Table 6-1 Dose Modification Guidelines for Specific Toxicities

NCI CTCAE Category	Severity	Action on Study Drug
Hematologic ANC	Febrile neutropenia	Hold dosing on Day 1 of Cycles ≥ 2 up to 3 weeks until febrile neutropenia is resolved, then resume dosing as appropriate. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	ANC < 1500 cells/μL on Day 1 of Cycles ≥ 2	Initiation (Day 1) of Cycles ≥ 2 should be delayed for up to 3 weeks until the ANC is ≥ 1500 cells/μL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	Grade ≥ 3 neutropenia lasting more than 7 days	Initiation (Day 1) of Cycles ≥ 2 should be delayed until the ANC is ≥ 1500 cells/μL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
Hematologic Platelets	Platelet count < 100,000/μL on any dosing day of Cycles ≥ 2	Dosing in Cycles ≥ 2 should be delayed for up to 3 weeks until the platelet count is ≥ 100,000 cells/μL. Dose of chemotherapy may be reduced by 1 dose level as appropriate.
	Grade 4 thrombocytopenia lasting more than 7 days or platelet count < 25,000 cells/μL at any time	Dosing in Cycles ≥ 2 should be delayed until the platelet count is ≥ 100,000 cells/μL. Dose of chemotherapy may be reduced by 1 dose level as appropriate.

Table 6-1 Dose Modification Guidelines for Specific Toxicities

NCI CTCAE Category	Severity	Action on Study Drug
Hematologic Anemia	≥ Grade 1	No dose modification is allowed for anemia. Transfusion and/or erythropoietin may be given as clinically indicated for the treatment of anemia (see Section 6.9.2).
Nausea, emesis, or diarrhea despite maximal prophylaxis	≥ Grade 3	On days that both chemotherapy and MLN4924 are administered, hold all dosing for up to 3 weeks or until the toxicity returns to ≤ Grade 1, and restart at the next lower dose of chemotherapy. On days when MLN4924 is given as a single agent, hold dosing of MLN4924 for up to 3 weeks or until the toxicity returns to ≤ Grade 1 before dosing is resumed. If treatment is delayed by more than 3 weeks, all treatments must be discontinued, and the patient comes off of the study. NOTE: Please ensure that optimal prophylaxis has been employed before dose reduction. Supportive care with moderate or strong CYP3A inhibitor/inducer should be avoided.
Stomatitis	≥ Grade 3	Hold treatment for up to 3 weeks until the stomatitis is ≤ Grade 1. If the stomatitis is not ≤ Grade 1 in 3 weeks, discontinue treatment. If acute ≥ Grade 3 stomatitis occurs at any time, the dose of chemotherapy should be reduced 1 level. This is a permanent dose reduction.
Hepatic toxicity	ALT/AST ≥ Grade 3 at any time	If ALT or AST is ≥ Grade 3 at any time, withhold MLN4924 dosing until patient has recovered to ≤ Grade 1 (see Section 6.4.2 for further details on dose modification of MLN4924). In addition, if toxicity is felt to be attributable to the chemotherapy agent(s), consider dose reduction for chemotherapy also by 1 dose level.
Hepatic toxicity	Total bilirubin > 1.5 × ULN, regardless of AST/AST	Hold all dosing for up to 3 weeks until bilirubin returns to within normal range and/or dose reduce chemotherapy by 1 level and/or modify MLN4924 dose (see Section 6.4.2).
Cardiac toxicity	Symptomatic arrhythmia during infusion	Stop infusion and manage arrhythmia according to institutional guidelines. Report as AE and discontinue further dosing.
Cardiac toxicity	Chest pain and/or symptomatic hypotension (< 90/60 mmHg)	Stop infusion. Perform an ECG. Give IV diphenhydramine and dexamethasone if hypersensitivity is thought to be the etiology. Also, consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. If > Grade 3, the patient comes off the study.
Neurotoxicity (paclitaxel or docetaxel only)	≥ Grade 2	Hold treatment until patient recovers to Grade 1 toxicity then resume treatment at the next lower dose level. This will be a permanent dose reduction. Carboplatin or MLN4924 are not to be dose modified.

Table 6-1 Dose Modification Guidelines for Specific Toxicities

NCI CTCAE Category	Severity	Action on Study Drug
Allergic reaction (paclitaxel or docetaxel only	Moderate symptoms	Stop infusion. Give IV diphenhydramine 25-50 mg and IV dexamethasone 10 mg and/or treatment per institutional guidelines. Resume infusion after recovery of symptoms at a low infusion rate. If no further symptoms, resume full dose rate until infusion is complete. If symptoms recur, stop infusion and discontinue patient.
Allergic reaction (paclitaxel or docetaxel only)	Severe symptoms	Stop infusion. Give IV diphenhydramine and dexamethasone and/or treatment per institutional guidelines as above. Add epinephrine or bronchodilators if indicated. Report as an AE and discontinue patient.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CYP=cytochrome P450; ECG=electrocardiogram; IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of the normal range.

6.4.2 Dose Modification Guidelines for MLN4924

- Patients will receive MLN4924 in combination with SoC at a dose regimen informed from Study C15010. If dosing with MLN4924 is held for toxicity during any given cycle, dosing may resume within that same cycle when toxicity is resolved (ALT/AST to ≤ Grade 1 or bilirubin within normal range). Alternatively, dosing may be held until the next cycle (in combination with SoC). Start of the next cycle may also be delayed for up to 2 weeks to allow patients to recover from any safety concerns, so that MLN4924 may be administered in combination with SoC. For patients who take treatment breaks at the investigator's discretion, patient eligibility for continued treatment, including all Day 1 predose assessments specified in the Schedules of Events, will be confirmed by the investigator before resumption of treatment. Treatment breaks must be no longer than 2 weeks in duration (4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively.

- In general, no dose reduction of MLN4924 is permitted. However, if toxicity is not resolved by the dose delays described in the bullet point above, and the patient is judged by the investigator to derive clinical benefit (SD or better) from continued treatment, the dose of MLN4924 may be reduced after discussion with and permission from the project clinician or designee.

6.5 Excluded Concomitant Medications and Procedures

6.5.1 Excluded Concomitant Medications and Procedures (Part A)

Medications that are prohibited in Part A are listed in Table 6-2.

Table 6-2 Excluded Concomitant Medications and Procedures During Part A

Drug Class/Therapy	Drug Name
Antiarrhythmics	Digoxin, dofetilide, quinidine, disopyramide
Anticoagulants	Warfarin
Antihistamines	Astemizole, terfenadine
Antipsychotics	Pimozide
Benzodiazepines	Alprazolam, diazepam, midazolam, triazolam, clobazam
Calcium channel blockers	Dihydropyridines (including felodipine and nisoldipine),verapamil
Gastrointestinal motility agents	Cisapride
HMG CoA-reductase inhibitors	Atorvastatin, cerivastatin, lovastatin, simvastatin
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus
Oral hypoglycemics	Tolbutamide, glyburide, glipizide, repaglinide
Proton pump inhibitors	Lansoprazole (Prevacid®), omeprazole (Prilosec®)
Others	Methadone, levacetylmethadol (levomethadyl), ergotalkaloids, halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, fluticasone, trimetrexate, cilostazol, eletriptan, fentanyl, losartan, celecoxib, S-mephenytoin
Acetaminophen and acetaminophen-containing products	
Any investigational agent other than MLN4924	
Known BCRP substrates	ie, methotrexate and sulfasalazine
Known BCRP inhibitors	ie, cyclosporine and eltrombopag (Promacta)
Moderate and strong CYP3A4 inhibitors and clinically significant CYP3A4 inducers	See Section 15.7
Known P-gp inhibitors	ie, **azithromycin (Zithromax),** captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor

Abbreviations: BCRP=breast cancer-resistance protein; CYP=cytochrome P450; P-gp=P-glycoprotein.
This list is not all-inclusive; please consult the fluconazole or itraconazole prescribing information for additional information regarding precautions, warnings, and contraindications.

6.5.2 Excluded Concomitant Medications and Procedures (Part B)

Medications and procedures that are prohibited in Part B are listed in Table 6-3.

Table 6-3 Excluded Concomitant Medications and Procedures During Part B

Therapy	Comment
Acetaminophen and acetaminophen-containing products	May be used judiciously in Part B and should not exceed a dose of 2 g in 24 hours
Amiodarone	Excluded within 6 months before the first dose of MLN4924 and during the study
Azole antifungal agents	Generally excluded during the study but voriconazole and fluconazole may be used as specified in Table 6-5
Any investigational agent other than MLN4924	Excluded during the study
Known BCRP inhibitors (ie, cyclosporine and eltrombopag [Promacta])	Generally excluded during the study but may be used as specified in Table 6-5
Clinically significant CYP3A4 inducers	Excluded within 14 days before dosing with MLN4924 and during the study (Section 15.7)

Abbreviations: BCRP=breast cancer-resistance protein; CYP=cytochrome P450.

6.6 Permitted Concomitant Medications and Procedures

6.6.1 Permitted Concomitant Medications and Procedures (Part A)

Medications and procedures that are specifically permitted during Part A are listed in Table 6-4.

Table 6-4 Permitted Concomitant Medications and Procedures During Part A

Therapy	Comment
Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs	Whenever possible, caution should be used with nephrotoxic concomitant medications (Section 15.2). Alternative concomitant non-nephrotoxic medications should be used whenever possible.
Red blood cell transfusion	For all patients with anemia, and especially for patients with hemoglobin values < 9 g/dL during the conduct of the study, consideration should be given for red blood cell transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines. Red blood cell transfusions must be administered before administration of study drug. Each transfusion episode, including the type of transfusion (red blood cell), should be recorded.

6.6.2 Permitted Concomitant Medications and Procedures (Part B)

Medications and procedures that are specifically permitted during Part B are listed in Table 6-5.

Table 6-5 Permitted Concomitant Medications and Procedures During Part B

Therapy	Comment
Azole antifungal agents	Permitted only if the patient's clinical condition requires the use of an azole antifungal agent. The patient may receive voriconazole and fluconazole from 24 hours after the last MLN4924 dose to 72 hours before the next MLN4924 dose. For example, if a patient receives MLN4924 on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then an azole may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Known BCRP substrates (ie, methotrexate and sulfasalazine) and known BCRP inhibitors (ie, cyclosporine and eltrombopag [Promacta])	Permitted only if the patient's clinical condition requires the use of a known BCRP substrate/inhibitor. The patient may receive it from 24 hours after the last MLN4924 dose to 72 hours before the next MLN4924 dose. For example, if a patient receives MLN4924 on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the BCRP substrate/inhibitor may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs	Whenever possible, caution should be used with nephrotoxic concomitant medications (Section 15.2). Alternative concomitant non-nephrotoxic medications should be used whenever possible.
Known P-gp inhibitors (ie, **azithromycin [Zithromax],** captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor)	Permitted only if the patient's clinical condition requires the use of a known P-gp inhibitor. The patient may receive it from 24 hours after the last MLN4924 dose to 72 hours before the next MLN4924 dose. For example, if a patient receives MLN4924 on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the P-gp inhibitor may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Red blood cell transfusion	For all patients with anemia, and especially for patients with hemoglobin values < 9 g/dL during the conduct of the study, consideration should be given for red blood cell transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines. Red blood cell transfusions must be administered before administration of study drug (ie, at least 1 day before dosing). Each transfusion episode, including the type of transfusion (red blood cell), should be recorded.

Abbreviation: BCRP=breast cancer-resistance protein; P-gp=P-glycoprotein.

6.7 Precautions and Restrictions

Concomitant medications and procedures that are excluded or must be used with caution are described in Section 6.5 and Section 6.6, respectively.

Certain situations may warrant further caution, such as modifying the dose of study drug(s). Dose modification guidelines are provided in Section 6.4.

6.7.1 MLN4924

It is not known what effects MLN4924 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below and in Section 15.10.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- As of Amendment 2, if they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing of the ICF through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only [as of Amendment 2], and lactational amenorrhea [as of Amendment 2] are not acceptable methods of contraception. Female and male condoms should not be used together.)

As of Amendment 2, female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

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

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only [as of

Amendment 2], and lactational amenorrhea [as of Amendment 2] are not acceptable methods of contraception. Female and male condoms should not be used together.)

As of Amendment 2, male patients must agree to not donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

6.7.2 Fluconazole

Pregnancy

Fluconazole single 150-mg tablet when used for candidiasis is classified as Pregnancy Category C. For all other indications, fluconazole is classified as Pregnancy Category D.

> *Use in Pregnancy: There are no adequate and well-controlled studies of DIFLUCAN in pregnant women. Available human data do not suggest an increased risk of congenital anomalies following a single maternal dose of 150 mg. A few published case reports describe a rare pattern of distinct congenital anomalies in infants exposed in utero to high dose maternal fluconazole (400–800 mg/day) during most or all of the first trimester. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These effects are similar to those seen in animal studies. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus (See PRECAUTIONS, Pregnancy).*[(8)]

Geriatric Use

> *Of the most frequently reported (> 1%) side effects, rash, vomiting, and diarrhea occurred in greater proportions of older patients.*
>
> *Controlled clinical trials of fluconazole did not include sufficient numbers of patients aged 65 and older to evaluate whether they respond differently from younger patients in each indication. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.*[(8)]

Please refer to the DIFLUCAN USPI for more information.

6.7.3 Itraconazole

Pregnancy

Itraconazole is a pregnancy Category C drug. Please refer to the itraconazole USPI[10] for more information.

> *Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5–20x MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10x MRHD). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.*
>
> *There are no studies in pregnant women. SPORANOX should be used in pregnancy only if the benefit outweighs the potential risk.*
>
> *During post-marketing experience, cases of congenital abnormalities have been reported. (See ADVERSE REACTIONS: Post-marketing Experience.)*[10]

Geriatric Use

> *Transient or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see BOX WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions). Itraconazole should be used with care in elderly patients (see PRECAUTIONS).*[10]

6.7.4 Docetaxel

Pregnancy

TAXOTERE is a pregnancy Category D drug. Please refer to the TAXOTERE USPI for more information.

> *TAXOTERE can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryofetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryofetal effects in animals occurred at doses as low as 1/50 and 1/300 the recommended human dose on a body surface area basis.*

There are no adequate and well-controlled studies in pregnant women using TAXOTERE. If TAXOTERE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE.[(11)]

Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

Please see the Docetaxel USPI[(11)] for additional information on geriatric use in different types of cancer.

6.7.5 Carboplatin

Pregnancy

Carboplatin is a pregnancy Category D drug. Please refer to the Carboplatin Injection USPI for more information.

Carboplatin Injection may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.[(12)]

Geriatric Use

Of the 789 patients in initial treatment combination therapy studies (NCIC and SWOG), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. In a combined database of 1,942 patients (414 were ≥65 years of age) that received single-agent carboplatin for different tumor types, a similar incidence of adverse events was seen in patients 65 years and older and in patients less than 65. Other reported clinical experience has not

identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal function is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage (see DOSAGE AND ADMINISTRATION).

Please see the Carboplatin USPI[12] for additional information.

6.7.6 Paclitaxel

Pregnancy

Paclitaxel is a pregnancy Category D drug. Please refer to the Paclitaxel Injection USPI for more information.

Paclitaxel Injection, USP can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths.

Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If Paclitaxel Injection, USP, is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.[13]

Geriatric Use

Of 2228 patients who received paclitaxel in eight clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients

treated with paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group.

Please see the Paclitaxel USPI[13] for additional information.

6.8 Guidance for Clinical Assessment and Management of Hemodynamic Compromise (Part A and Part B)

It is essential that the patient is carefully evaluated at screening and before each MLN4924 dose for early symptoms and signs of hemodynamic compromise and active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration.

For those patients for whom there is a concern of dehydration, the following guidance for rehydration before MLN4924 dosing may be considered: 500 mL/hour of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate; each infusion of IV fluids should be recorded in the electronic case report forms (eCRFs).

For all patients with anemia, and especially for patients with hemoglobin values < 9 g/dL at screening or during the conduct of the study, red blood cell transfusions should be considered before MLN4924 dosing based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines; each red blood cell transfusion should be recorded in the eCRFs.

Patients who experience signs and symptoms of hemodynamic compromise after MLN4924 dosing (eg, tachycardia, hypotension, orthostasis, changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization as clinically indicated.

Patients who experience an untoward reaction with MLN4924 should be followed closely on subsequent dosing.

6.9 Management of Clinical Events

Specific recommendations for the management of MLN4924 clinical events that were identified from toxicology studies in dogs and rats and from early experience in ongoing clinical studies are outlined in the MLN4924 IB and DCSI.

The most common adverse drug reactions for docetaxel and carboplatin+paclitaxel are described in Section 1.6. Refer to the applicable USPIs for additional details regarding the management of clinical events attributed to these agents.

Patients who experience an AE with MLN4924 should be followed closely for a recurrence of similar or other AEs upon subsequent dosing of MLN4924.

6.9.1 Guidance for Use of Granulocyte-Colony Stimulating Factor

Use of growth factors such as granulocyte-colony stimulating factor (G-CSF) are permitted at the investigator's discretion. If G-CSF is used, it should be used in accordance with the Revised American Society of Clinical Oncology guidelines.[16]

6.9.2 Guidance for Clinical Assessment and Management of Anemia

Transfusion and/or erythropoietin may be given as clinically indicated for the treatment of anemia. These should be recorded in the eCRFs.

For all patients with anemia, and especially for patients with hemoglobin values < 9 g/dL at screening or during the conduct of the study, red blood cell transfusions should be considered before MLN4924 dosing based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines; each red blood cell transfusion should be recorded in the eCRFs. Transfusions should be conducted before study drug administration (ie, at least 1 day before dosing).

Use of Erythropoietin

Use of erythropoietin may be considered per the investigator's discretion and per institutional guidelines.

6.10 Blinding and Unblinding

This is an open-label study.

6.11 Description of Investigational Agents

6.11.1 MLN4924

The drug product is labeled MLN4924 (MLN4924-003 concentrate for solution for infusion).

The formulation consists of 10 mg/mL MLN4924-003 (as free base) in a solution containing citric acid, sulfobutylether-beta-cyclodextrin, and sodium hydroxide. Each USP Type I glass vial nominally contains 5 mL of compounded sterile solution, sealed with a coated butyl rubber stopper, and oversealed with an aluminum seal with a plastic cap.

MLN4924-003 concentrate for solution for infusion Drug Product is formulated with the following excipients: citric acid, sulfobutylether-beta-cyclodextrin, sodium hydroxide, and water for injection.

Details are available in the MLN4924 IB.

6.11.2 Fluconazole

Fluconazole is a synthetic triazole antifungal agent available as tablets for oral administration. Fluconazole Tablets USP contain 200 mg of fluconazole USP and are commercially available in 100 count bottles. Please refer to the fluconazole USPI.

The precautions, warnings, contraindications, and AEs associated with fluconazole therapy are included in the fluconazole USPI.

6.11.3 Itraconazole

SPORANOX® (itraconazole) Oral Solution is a synthetic triazole antifungal agent. SPORANOX® contains 10 mg of itraconazole per mL, solubilized by hydroxypropyl-β-cyclodextrin (400 mg/mL) as a molecular inclusion complex. SPORANOX® Oral Solution is commercially available in bottles containing 150 mL. Please refer to the SPORANOX® USPI.

The precautions, warnings, contraindications, and AEs associated with itraconazole therapy are included in the itraconazole USPI.

6.11.4 Docetaxel

Docetaxel is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Please refer to the docetaxel USPI.

6.11.5 Carboplatin

Carboplatin is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Please refer to the carboplatin USPI.

6.11.6 Paclitaxel

Paclitaxel is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Please refer to the paclitaxel USPI.

6.12 Preparation, Reconstitution, and Dispensation

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

MLN4924, docetaxel, carboplatin, and paclitaxel are anticancer drugs, and as with other potentially toxic compounds, caution should be exercised when handling MLN4924 and chemotherapy agents.

6.12.1 MLN4924

The specified number of MLN4924-003 concentrate for solution for infusion Drug Product vials should be removed and allowed to equilibrate to room temperature before dilution. Using aseptic technique, the specified amount of drug product solution should be removed and administered using a 250-mL 5% dextrose solution. For detailed instructions for the preparation of the infusion, refer to the Pharmacy Manual. The MLN4924 (MLN4924-003 concentrate for solution for infusion) prepared IV bag must be used within 6 hours. The vial must not be shaken at any time during dose preparation. The bag, needle, and syringe must be disposed of in a proper biohazard container.

Detailed reconstitution and dosage preparation instructions are provided in the Pharmacy Manual.

6.12.2 Docetaxel, Carboplatin, and Paclitaxel

Please refer to the USPIs for the SoCs (docetaxel, carboplatin, and paclitaxel) for instructions and precautions regarding preparation.

6.13 Packaging and Labeling

6.13.1 MLN4924

MLN4924 (MLN4924-003 concentrate for solution for infusion) will be provided in 10-mL USP Type I glass vials nominally containing 5 mL of compounded sterile solution at a concentration of 10 mg/mL (as free base), sealed with a coated butyl rubber stopper, and oversealed with an aluminum seal with a plastic cap.

6.13.2 Fluconazole

Fluconazole will be provided by Millennium Pharmaceuticals, Inc. (Millennium) as generic, 200-mg fluconazole tablets USP that are commercially available in 100-count bottles. As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the Study Manual.

6.13.3 Itraconazole

Itraconazole will be provided by Millennium as SPORANOX® Oral Solution, which is commercially available in bottles containing 150 mL. As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the Study Manual.

6.13.4 Docetaxel, Carboplatin, and Paclitaxel

Docetaxel, carboplatin, and paclitaxel may be sourced locally by the clinical sites when arrangements have been made and agreed to by Millennium and the clinical site and when regulations allow for clinical site sourcing, appropriate labeling, and compliance with local and regional regulations. As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the Study Manual.

6.14 Storage, Handling, and Accountability

6.14.1 MLN4924

Vials of MLN4924 (MLN4924-003 concentrate for solution for infusion) are to be stored at 2°C to 8°C.

All investigational supplies are to be kept in a secure area with controlled access.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Disposal instructions are provided in the Pharmacy Manual.

6.14.2 Fluconazole

Fluconazole 200-mg Tablets USP must be kept in the original bottle and stored at 20°C to 25°C (68°F-77°F). All investigational supplies are to be kept in a secure area with controlled access.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Disposal instructions are provided in the Pharmacy Manual.

6.14.3 Itraconazole

SPORANOX® Oral Solution must be kept in the original bottle until it is time to take it. Keep the SPORANOX® Oral Solution in a cool, dry place where the temperature is at or below 25°C (77°F). Do not freeze. All investigational supplies are to be kept in a secure area with controlled access.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Disposal instructions are provided in the Pharmacy Manual.

7. STUDY CONDUCT

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

7.1 Study Personnel and Organizations

The contact information for the project clinician for this study, clinical pharmacologist, the central laboratory and any additional clinical laboratories, contract research organization team, and other vendors can be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

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

7.3 Treatment Group Assignments

7.3.1 Drug-Drug Interaction Assessment (Part A)

The first 4 to 8 patients will be assigned to the Fluconazole Arm (moderate CYP3A inhibitor). After review of the emerging data (see Section 8.1.12 for details of interim analyses), the investigator will recommend each patient to the Fluconazole Arm (MLN4924+fluconazole) or the first cohort in the Itraconazole Arm (8-mg/m^2 MLN4924+itraconazole), and the patient will be assigned to the appropriate arm by the sponsor based on slot availability until enrollment in each arm is filled.

Enrollment into the Itraconazole Arm, Safety Lead-in 15-mg/m^2 MLN4924 Cohort, added per Amendment 1, may begin once the amendment is approved at the clinical site. Enrollment into the Itraconazole Arm, 20-mg/m^2 MLN4924 Cohort, also added per Amendment 1, may begin once the Part A PK and safety data from 3 PK-evaluable patients in the safety lead-in cohort have been reviewed and the sponsor has confirmed that the anticipated safety margin for the 20-mg/m^2 dose is adequate.

In Part A, Day 8 dosing of MLN4924 should not be delayed or missed. If the Day 8 dosing is delayed or missed, then the patient will not be considered PK evaluable and will be replaced.

All doses of fluconazole or itraconazole must be taken per the Schedules of Events. If any dose is missed, the patient will not be considered PK evaluable and will be replaced.

7.3.2 Continued Treatment With MLN4924 in Combination With Standard of Care (Part B)

Investigators may assign each patient to 1 of the 2 combination regimens (MLN4924+docetaxel or MLN4924+carboplatin+paclitaxel) in Part B based on their medical judgment after a washout period of at least 2 weeks (and up to 8 weeks) from the last dose of fluconazole or itraconazole to allow patients to recover from any safety concerns and to confirm that the patient is eligible to participate in Part B. Participation in Part B of the study is optional. Any patient who continues on to Part B will need to be re-evaluated for entry criteria (see Section 7.4.20) before treatment in Part B can begin.

7.4 Study Procedures

The timing of the study procedures outlined in the following subsections is provided in the Schedules of Events. When applicable, specific visit windows for assessments are provided in the footnotes to the study schedules.

In Part B, dosing of MLN4924 on Days 1, 3, or 5 (of any cycle) may be delayed by up to 2 days (Cycles 1 through 12) or up to 2 weeks (after completion of Cycle 12; up to 4 weeks after consulting with the sponsor) to accommodate inclement weather, holidays, vacations, or other administrative reasons; treatment breaks may not be taken consecutively.

Refer to the Schedules of Events for timing of assessments.

- Schedule of Events for Drug-Drug Interaction (Part A)
- Serial Pharmacokinetic Sample Breakdown
- Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 1 Through Cycle 12
- Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 13 and Beyond (as of Amendment 2)

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 (Part A)

During screening, a complete medical history will be compiled for each patient in Part A. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it (see inclusion criterion 2, Section 5.1). Concomitant medications will be recorded as specified in Section 7.4.11.

7.4.4 Physical Examination

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

7.4.5 Patient Height

Height will be measured during screening only.

7.4.6 Patient Weight

Weight will be measured as indicated in the Schedules of Events. On dosing days, weight will be measured before dosing of MLN4924.

7.4.7 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group PS (Section 15.4) will be assessed as indicated in the Schedules of Events (see inclusion criterion 5, Section 5.1).

7.4.8 Echocardiogram or Radionuclide Angiography (Part A)

Left ventricular ejection fraction should be assessed by echocardiogram or radionuclide angiography at screening in Part A only.

7.4.9 Vital Signs

Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature, will be collected as indicated in the Schedules of Events and as clinically indicated. All vital signs will be measured in the sitting position (and/or supine after completion of Cycle 12) as noted in the Schedules of Events.

In addition, during Part A at predose and 1 hour postdose of MLN4924 administration on Day 1 and Day 8, orthostatic blood pressure and heart rate measurements will be measured with the patient in a supine position and then standing, after waiting for approximately 3 to 4 minutes. In Part B, orthostatic blood pressure and heart rate measurements will be taken on Cycle 1, Day 1 only, per the Schedules of Events.

When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection unless otherwise noted in the Schedules of Events.

7.4.10 Pregnancy Test (Part A)

A serum pregnancy test will be performed for women of childbearing potential at screening in Part A only. The results from this test must be available and negative before the first dose of study drug.

7.4.11 Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded from the time of the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s). See Section 6.5 and Section 6.6 for additional details regarding excluded and permitted concomitant medications and procedures.

7.4.12 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedules of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.13 Enrollment

Enrollment is achieved when the first dose of any study drug has been administered.

Procedures for completion of the enrollment information are described in the Pharmacy and Study Manuals.

7.4.14 Electrocardiogram

A 12-lead ECG will be performed as indicated in the Schedules of Events. When the timing ECG assessment coincides with the timing of a blood draw, ECG assessments will be

completed before blood sample collection unless otherwise noted in the Schedules of Events.

The ECGs performed after infusion should be reviewed by the investigator or designee before the patient leaves the clinic.

7.4.15 Clinical Laboratory Evaluations

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

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

Serum Chemistry

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

a No longer required after completion of Cycle 12 (as of Amendment 2).

Coagulation

Part A Screening

- Prothrombin time international normalized ratio
- Activated partial thromboplastin time
- Fibrinogen
- D-dimer

Part B

If the initial coagulation screen is positive (ie, results are outside of the laboratory's

Coagulation

normal range) in Part A, coagulation studies in Part B should include a full coagulation panel. If the initial coagulation screen is negative (ie, results are within the laboratory's normal range) in Part A, then no further coagulation studies need to be done.

Urinalysis With Microscopic Analysis

- Turbidity and color
- pH
- Specific gravity
- Protein
- Phosphate[a]
- Ketones
- Bilirubin
- Occult blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes
- Microscopic assessment

a Included after completion of Cycle 12 (as of Amendment 2).

7.4.16 Disease Assessment (Part B)

Computed tomography scans with IV contrast (unless medically contraindicated) or MRI of the chest, abdomen, and pelvis will be performed as entry criteria for Part B.

Computed tomography scans with IV contrast encompassing the known sites of disease will also be performed at the end of Cycle 2, end of Cycle 4, and at the end of every other cycle (Cycles 1-12), or after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 2) thereafter. Additional CT scans may be performed, per investigator's discretion, if clinically indicated. A scan should be taken at the EOS visit if a scan has not been completed within the past 28 days.

If CT scan does not provide adequate imaging, MRI may be used to evaluate sites of disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1, Day 1, then the results of those scans may be used for the entry criteria for Part B. For each site of disease, the imaging modality (CT or MRI) used at entry criteria for Part B must be used throughout the study. Tumor response will be assessed by the investigator at these times using RECIST, version 1.1.[(14)]

7.4.17 Pharmacokinetic Measurements

During Part A of the study, for both the Fluconazole and Itraconazole Arms, serial blood samples (approximately 3 mL each) will be collected from each patient for the determination of MLN4924 plasma concentrations before and after the start of MLN4924 infusion on Day 1 (when administered alone) and Day 8 (when co-administered with fluconazole or itraconazole) at the time points indicated in the Serial Pharmacokinetic Sample Breakdown.

Four additional blood samples for the determination of MLN4924 concentrations in whole blood will be drawn following MLN4924 infusion on Day 1 only.

The timing, but not the number, of PK blood samples may be changed if emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK of MLN4924. To ensure that the measurements are representative of plasma exposure, blood draws will be conducted in the arm opposite to a patient's IV infusion. If only a single arm is available, blood should be drawn as distal to the site of the IV infusion as feasible, and the site of the blood draw should be documented.

The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, and particular care should be given to recording blood sampling times that occur close to the infusion.

Details regarding the preparation, handling, and shipping of samples are provided in the Study and Laboratory Manuals.

For patients who experience hypersensitivity or a hepatic, cardiac, or renal SAE considered by the investigator to be at least possibly related to study drug, an additional blood sample should be collected, if clinically feasible, for the determination of MLN4924 plasma concentration as close to the onset of the event as possible.

If deemed appropriate, the blood samples collected in this study may be analyzed to determine plasma concentrations of MLN4924 major metabolites in humans. Also, if considered necessary to verify treatment assignments, a subset of the samples may be used for measurement of concentration of the co-administered drugs (fluconazole or itraconazole).

7.4.18 Pharmacodynamic Measurements

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Blood samples will be collected during screening and at the time points indicated in the Serial Pharmacodynamic Sample Breakdown following MLN4924 dosing on Days 1 and 8.

The timing, but not the number, of blood samples may be changed if emerging data indicate that an alteration in the sampling scheme is needed to better characterize the pharmacodynamic effects of MLN4924.

Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.4.19 Patient Diary

Patient instructions regarding the CYP3A inhibitor dosing schedule, study drug handling, use of the patient diary, visit expectations, diary review and return of study drug containers and unused study drug will be provided on Day 4 of Part A before dosing with the CYP3A inhibitor.

Patients are to be instructed to bring their diaries and study drug to the clinic on the Day 8 visit of Part A, and all entries are to be reviewed by study staff with the patient. If the patient misses any dose of the CYP3A inhibitor, they will not be considered PK evaluable and will be replaced (see Section 8.1.4). Understanding of and compliance with instructions should be continually evaluated and addressed as needed throughout trial participation.

7.4.20 Entry Criteria for Continuation Into Part B

For patients to be eligible for dosing with MLN4924+SoC (Part B), they must meet the following entry criteria:

- Eastern Cooperative Oncology Group PS of 0 to 1
- Laboratory values for hemoglobin, ANC, platelet, total bilirubin, ALT, AST, ALP, and serum creatinine or calculated/measured creatinine clearance as specified in Section 5.1
- Diarrhea symptoms resolved to Grade 1 or better
- Rate-corrected QT interval of electrocardiograph < 500 msec
- Computed tomography scan or MRI of the chest, abdomen, and pelvis within 28 days of Cycle 1 Day 1

In addition, patients will require at least a 2-week (may be extended up to 8 weeks) washout period after their last dose of fluconazole or itraconazole. For patients to begin dosing in Part B, their predose Cycle 1, Day 1 assessments in Part B must return to the baseline values of Part A (or ≤ Grade 1) or to a level considered acceptable by the investigator after discussion with the project clinician or designee. If, after a maximum of 8 weeks from the last dose in Part A (eg, up to 8 weeks after the Day 10 visit), the predose Cycle 1, Day 1 assessments in Part B have not returned to Part A baseline values (or ≤ Grade 1), the patient will not be eligible for dosing with MLN4924+SoC, and all assessments required for the EOS visit should be completed. The predose Cycle 1, Day 1 assessments for Part B do not need to be repeated if the Day 24 Part A results confirm that the patient is eligible for dosing in Part B AND Cycle 1, Day 1 occurs within 5 days from Part A Day 24; however, the LFTs will need to be repeated within 3 days of Cycle 1, Day 1.

7.5 Completion of Study

Part A

Patients will be considered to have completed Part A of the study if they have completed the protocol-specified assessments within Part A (ie, MLN4924+fluconazole or MLN4924+itraconazole) of the protocol.

An EOS visit is needed in Part A only if the patient does not continue into Part B for any reason. The EOS visit will include physical examination (including ECOG PS and vital signs), laboratory assessments (hematology, chemistry, and urinalysis), and 12-lead ECG. The EOS visit will be conducted 30 (+ 10) days after the last dose of study drug in Part A. If the EOS visit occurs before 30 days after the last dose of MLN4924, patients should be contacted via telephone on Day 30 to assess for any new or ongoing AEs or SAEs that may have occurred since the previous visit.

Part B

Patients will be considered to have completed Part B of the study if they discontinue treatment for any of the reasons outlined in Section 7.6. The EOS visit will be conducted 30 (+ 10) days after the last dose of study drug in Part B. If the EOS visit occurs before 30 days after the last dose of MLN4924, patients should be contacted via telephone on Day 30 to assess for any new or ongoing AEs or SAEs that may have occurred since the previous visit.

7.6 Discontinuation of Treatment with Study Drug, and Patient Replacement

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

- Adverse event
- Protocol violation
- Progressive disease
- 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 EOS visit will be completed as specified in the Schedules of Events. The primary reason for study drug discontinuation will be recorded on the eCRF. In both arms of Part A of the study, patients who are not PK evaluable (see Section 8.1.4) will be replaced.

Note: In Part B of the study, patients may receive MLN4924 until they experience PD or unacceptable MLN4924-related toxicities or discontinue treatment for any reason.

Patients who have achieved objective clinical benefit from combination therapy (SoC plus MLN4924) AND who have developed intolerance that is reasonably attributable to the SoC after 4 or more cycles may continue on single-agent MLN4924 at the same dose and schedule upon request by the investigator and agreement by the sponsor.

7.7 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
- Completed study
- Death
- Other
- Progressive disease

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.

7.8 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.

The clinical team and the clinical research associate will review treatment compliance during investigational visits and at the completion of the study. Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable within a 2-day (Cycles 1 through 12) to a 4-week (after completion of Cycle 12) window for holidays, vacations, and other administrative reasons (see Section 6.4.2); treatment breaks may not be taken consecutively. If the study schedule is shifted, both assessments and dosing must be shifted to ensure that collection of assessments is completed before dosing. These 2-day to 4-week windows are allowed for Part B and do not apply for Part A.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. Analysis of variance (ANOVA) analysis will be conducted on log-transformed PK parameters, C_{max} and AUC, to estimate the magnitude of the DDI interaction. Summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous

variables, and the number and percentage per category for categorical data. A formal statistical analysis plan (SAP) will be developed and finalized before database lock.

8.1.1 Drug-Drug Interaction Assessment

Assessments for the DDI portion of the study (Part A) will include the following:

- For the MLN4924-fluconazole DDI assessment, the ratios of geometric mean C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of MLN4924 (in the presence of fluconazole on Day 8 vs in the absence of fluconazole on Day 1) and associated 2-sided 90% CIs will be calculated based on the within-patient variance calculated by ANOVA.

- For the MLN4924-itraconazole DDI assessment, the ratios of geometric mean C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of MLN4924 (in the presence of itraconazole on Day 8 vs in the absence of itraconazole on Day 1) and associated 2-sided 90% CIs will be calculated based on the within-patient variance calculated by ANOVA.

- Individual values and descriptive statistics of MLN4924 plasma concentration–time data and PK parameters will be listed and tabulated (see Section 8.1.8) by study day, in the presence and absence of the inhibitor (fluconazole or itraconazole).

8.1.2 Determination of Sample Size

It is anticipated that as many as approximately 52 patients will be enrolled in this study.

The sample size calculation is based on the expected 2-sided 90% CI for the difference in the paired, log transformed AUC (or C_{max}) means of MLN4924 on Day 1 (MLN4924 alone) and Day 8 (MLN4924 co-administered with CYP3A inhibitor). Based on the PK information obtained from Schedules B and C of Study C15001, the within-subject CV was estimated to be 0.12 for AUC and 0.17 for C_{max}, respectively. Assuming that the AUC (or C_{max}) ratio in the presence of fluconazole versus in the absence of fluconazole or in the presence of itraconazole versus in the absence of itraconazole is 2.0, with a sample size of 12 evaluable patients per arm, the 90% CI of the ratio of geometric means is expected to be (1.833, 2.182) for AUC and (1.759, 2.274) for C_{max} based on the above discussed variance assumptions. If the geometric mean AUC (or C_{max}) ratio is X, the corresponding 90% CI is expected to be (1.833X/2, 2.182X/2) (or [1.759X/2, 2.274X/2]).

In the Fluconazole Arm, approximately 12 PK-evaluable patients will be enrolled. In the Itraconazole Arm, approximately 12 PK-evaluable patients will be enrolled in the 8-mg/m^2

and 20-mg/m^2 MLN4924 cohorts, and 3 additional PK-evaluable patients will be needed in the safety lead-in cohort. A patient is PK-evaluable if he or she completes the protocol-specified dosing and PK assessments without dose reductions in Part A. Patients who are not PK evaluable (see Section 8.1.4) will be replaced. Assuming that 25% of the enrolled patients will not be PK evaluable, approximately 52 patients will be enrolled to provide the total intended number of PK-evaluable patients in each arm of Part A.

8.1.3 Randomization and Stratification

No randomization or stratification will be performed in this study.

8.1.4 Populations for Analysis

Safety population for Part A: All enrolled patients who receive at least 1 dose of MLN4924 during Part A. All safety and pharmacodynamic analyses in Part A will be performed using the safety population for Part A.

Safety population for Part B: All patients who continue to Part B and receive at least 1 dose of study drug during Part B. All safety analyses in Part B will be performed using the safety population for Part B.

Pharmacokinetic-Evaluable population: Patients who receive all protocol-specified dose regimens, did not receive any excluded medications throughout the completion of PK sampling, and have MLN4924 plasma concentration–time data to reliably estimate PK parameters based on noncompartmental analysis methods.

Response-Evaluable population: Patients who receive at least 1 dose of study drug in Part B, have measurable disease as entry criteria for Part B, and have at least 1 postbaseline disease assessment.

8.1.5 Procedures for Handling Missing, Unused, and Spurious Data

All available data will be included in data listings. In general, no imputation of values for missing data will be performed. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.6 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized descriptively, including age, sex, race, ethnicity, weight, height, body mass index, baseline disease characteristics, primary diagnosis, and other parameters as appropriate. Baseline characteristics will be defined separately for Part A and Part B.

8.1.7 Efficacy Analysis

Analysis of all efficacy measures collected from Part B will be descriptive. Disease response to MLN4924 in combination with SoC will be based on the best overall response as determined by the investigator using RECIST version 1.1 guidelines (Section 15.3). The duration of response will be defined in patients with disease response (complete response [CR] or PR) as the time between the first documentation of response and PD. Responders without PD will be censored at the last clinical assessment of response.

8.1.8 Pharmacokinetic Analysis

Individual values and descriptive statistics of MLN4924 plasma concentration–time data and PK parameters will be listed and tabulated by treatment arm and study day on Day 1 of Part A (MLN4924 alone) and Day 8 of Part A (MLN4924 co-administered with either fluconazole or itraconazole). Pharmacokinetic parameters of MLN4924 with and without the inhibitor (fluconazole or itraconazole) in individual patients will be calculated using noncompartmental methods. Pharmacokinetic parameters include, but are not limited to, C_{max}, T_{max}, $AUC_{0\text{-last}}$, $t_{1/2}$ (as permitted by the data), CL, V_{ss}, and $AUC_{0\text{-inf}}$ (as permitted by the data). The B/P ratio of MLN4924 will also be derived from plasma and whole blood concentration data.

Descriptive statistics of MLN4924 plasma concentration–time data and PK parameters will be tabulated by treatment arm and study day (ie, Day 1 or Day 8 with or without the inhibitor [fluconazole or itraconazole]). For each of the treatment arms, individual and mean MLN4924 plasma concentration data during Part A will be plotted over time on Day 1 and Day 8.

See Section 8.1.12 for information on the preliminary PK analysis.

8.1.9 Pharmacodynamic Analysis

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[redacted]

8.1.10 Pharmacokinetic-Pharmacodynamic Analysis

CCI

[redacted]

8.1.11 Safety Analysis

A safety analysis will be conducted separately for Part A and Part B to respectively characterize the safety profiles of MLN4924 co-administered with CYP3A inhibitors and MLN4924 in combination with SoC. The Safety population will be used for the safety analysis. Safety will be evaluated based on the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory values using the Safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

A treatment-emergent AE in Part A is defined as any AE that occurs after administration of the first dose of study treatment during Part A and up through 30 days after the last dose of study drug during Part A for patients who do not continue into Part B, or up through Part B Cycle 1 Day 1 (predose) for patients who continue into Part B, any event that is considered drug-related regardless of the start date of the event for patients who do not continue into part B, or any event that is present at baseline but worsens in severity during Part A.

A treatment-emergent AE in Part B is defined as any AE that occurs after administration of the first dose of study treatment during Part B and up through 30 days after the last dose of

study drug during Part B, or any event that is present at Part B baseline but worsens in severity during Part B.

Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities by System Organ Class, High-Level Term, and Preferred Terms and will include the following categories:

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

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

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients) will be tabulated by System Organ Class and Preferred Term. Tabulation also will be provided that enumerates AEs by maximum intensity. Deaths, SAEs, and AEs resulting in study drug discontinuation will be tabulated.

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

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the MLN4924 safety profile.

The number and percent of patients experiencing abnormal ECG results will be summarized over each time point, separately for Part A by DDI cohort, and for Part B by treatment arm.

Graphical displays will be used to show vital sign parameters over time, separately for Part A by DDI cohort, and for Part B by treatment arm. In addition, descriptive statistics will be tabulated for orthostatic hypotension and orthostatic heart rate.

All concomitant medications collected from screening throughout the study period will be classified to Preferred Terms according to the World Health Organization drug dictionary.

Additional safety analyses may be performed to enumerate rates of toxicities and to further define the safety profile of MLN4924.

8.1.12 Interim Analyses (Preliminary Drug-Drug Interaction Assessment, Part A)

No formal interim analysis is planned. There will be an ongoing review of safety data with the medical monitor and study investigators.

A preliminary PK analysis will be conducted after the first 4 to 8 patients have completed the Fluconazole Arm (MLN4924+fluconazole) of Part A. After review of the emerging data from the Fluconazole Arm, patient assignment to the first cohort in the Itraconazole Arm (8-mg/m^2 MLN4924+itraconazole) will be initiated. Dose modifications of MLN4924 in the Itraconazole Arm may be reconsidered based on the magnitude of the interaction with the moderate CYP3A inhibitor fluconazole and the ability to accurately estimate PK parameters for DDI evaluation.

Following completion of the first 3 patients in the Itraconazole Arm, 8-mg/m^2 MLN4924 Cohort, preliminary PK data will be reviewed to guide expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients. If these emerging preliminary PK data indicate that the magnitude of the interaction with the strong CYP3A inhibitor itraconazole reaches the anticipated approximately 10-fold change, and individual drug exposures do not exceed those seen at doses of MLN4924 ≥ 110 mg/m^2, then up to 3 additional patients to provide at least 4 to 6 PK-evaluable patients will be enrolled. If the magnitude of the interaction with the strong CYP3A inhibitor itraconazole is much greater than anticipated (greater than the predefined safety margin of 14-fold), with individual MLN4924 exposures exceeding those seen at doses of MLN4924 ≥ 110 mg/m^2, then no additional patients will be enrolled in the Itraconazole Arm of Part A.

As of the implementation of Amendment 1, following completion of Part A by 3 PK-evaluable patients in the Safety Lead-in 15-mg/m^2 MLN4924 Cohort, safety and PK data will be reviewed to inform expansion of the Itraconazole Arm to the total intended number of 12 PK-evaluable patients in the 20-mg/m^2 MLN4924 Cohort. If the preliminary PK data from the safety lead-in cohort indicate that the magnitude of the interaction between the proposed 20-mg/m^2 MLN4924 dose and the strong CYP3A inhibitor itraconazole would be greater than the predefined safety margin (5-fold, with individual MLN4924 exposures potentially exceeding those seen at doses of MLN4924 ≥ 110 mg/m^2), then no patients will be enrolled in the 20-mg/m^2 MLN4924 Cohort. Dosing with intermediate doses of MLN4924 and/or evaluation of the drug interaction with the moderate CYP3A inhibitor, fluconazole, may then be reconsidered if it is deemed necessary to further enhance our understanding of the effect of CYP3A inhibition on the PK of MLN4924.

9. STUDY COMMITTEES

9.1 Millennium Safety Assessments

Safety data will be reviewed and assessed periodically by a Global Pharmacovigilance team and a cross-functional Safety Management Team throughout the conduct of the study. These cross-functional reviews will include a Global Safety Lead from the study team, as well as other representation from other departments at Millennium such as Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, and Clinical Operations.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 Adverse Event Definition

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

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

10.1.3 Serious Adverse Event Definition

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

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

treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[15] 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.

10.2 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 10.3 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 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

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

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[(15)] 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?

10.3 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 first dose of study drug through 30 days (+ 10 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 (+ 10 days) 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).

10.4 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 10.2). 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 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 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.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

11.2 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.

11.3 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 (CD) or other electronic media will be placed in the investigator's study file.

11.4 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.

11.5 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.

11.6 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.

11.7 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.

11.8 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.

11.9 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.

11.10 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.

11.11 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 report this via the phone numbers or email address provided below. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

Call Center	Phone Number	Email	Fax
PPD			

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 PPD (refer to Section 10.2).

11.12 Closure of the Study

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

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

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, 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.

11.13 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.

12. USE OF INFORMATION

All information regarding MLN4924 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 MLN4924 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.

13. INVESTIGATOR AGREEMENT

I have read Protocol C15011 Amendment 2: A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A-Mediated Inhibition on the Pharmacokinetics, Safety, and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

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)

14. REFERENCES

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15. APPENDICES

15.1 Hematologic Toxicity of Carboplatin Alone and in Combination With Paclitaxel

In 2 prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada Clinical Trials Group and the SWOG, 789 chemotherapy-naïve patients with advanced ovarian cancer were treated with carboplatin or cisplatin in combination with cyclophosphamide every 28 days for 6 courses before surgical re-evaluation. See Table 15-1 for the hematologic adverse experiences of patients treated with carboplatin in combination with cyclophosphamide.

Table 15-1 Hematologic Adverse Experiences of in Patients With Ovarian Cancer Treated With Carboplatin in Combination With Cyclophosphamide

Adverse Experience	Laboratory Value	NCIC CTG Study % Patients (N=447)	SWOG Study % Patients (N=342)
Bone Marrow			
Thrombocytopenia	< 100,000/mm^3	70	59
	< 50,000/mm^3	41	22
Neutropenia	< 2000 cells/mm^3	97	95
	< 1000 cells/mm^3	81	84
Leukopenia	< 4000 cells/mm^3	98	97
	< 2000 cells/mm^3	68	76
Anemia	< 11 g/dL	91	88
	< 8 g/dL	18	8
Infections		14	18
Bleeding		10	6
Transfusions		42	25

Source: Carboplatin US Package Insert.[12]

Abbreviations: NCIC CTG=National Cancer Institute of Canada Clinical Trials Group; SWOG=Southwest Oncology Group.

In a randomized clinical trial, 798 patients with ovarian cancer were treated with either cisplatin/paclitaxel or paclitaxel/carboplatin therapy at 3-week intervals for 6 courses. See Table 15-2 for the hematologic adverse experiences of patients treated with paclitaxel/carboplatin.

Table 15-2 Hematologic Toxicities and Associated Supportive Care in Patients With Advanced Ovarian Cancer Stratified by Treatment Arm and Toxicity Grade

		NCI CTC Grade, %												Difference[a] in the Proportions of Patients With Grades 3/4 Toxicity, %	
		Paclitaxel/Carboplatin Arm						Cisplatin/Paclitaxel Arm							
Toxicity	**Set**	**N**	**0**	**1**	**2**	**3**	**4**	**N**	**0**	**1**	**2**	**3**	**4**	**E**	**95% CI**
Hemoglobin	C	2209	29.1	49.4	20.1	1.3	0.1	2095	33.6	49.5	16.1	0.8	0.0	-0.6	-1.3 to 0.0
	P	388	9.0	40.7	44.3	5.4	0.5	382	14.7	44.2	37.2	3.9	0.0	-2.0	-5.1 to 1.1
Platelets	C	2193	71.9	19.9	5.2	2.5	0.5	2082	93.4	6.2	0.2	0.2	0.0	**-2.9**	**-3.6 to -2.1**
	P	388	43.3	31.2	12.6	10.1	2.8	382	78.3	19.4	1.3	1.0	0.0	**-11.8**	**-15.3 to -8.4**
Transfusions pRBCs[a]	C	1868	94.3	--	--	5.7	--	1766	97.2	--	--	2.8	--	**-2.9**	**-4.2 to -1.6**
	P	383	81.7	--	--	18.3	--	370	89.5	--	--	10.5	--	**-7.7**	**-12.7 to -2.8**
Leukocytes	C	2200	37.0	22.6	29.3	10.8	0.3	2073	56.4	23.3	17.3	2.9	0.0	**-8.1**	**-9.6 to -6.6**
	P	388	13.4	16.0	38.7	30.4	1.5	382	31.4	35.1	32.7	10.5	0.3	**-21.2**	**-26.8 to -15.6**
Neutrophils	C	1842	56.9	12.9	12.8	12.4	5.0	1864	70.9	10.6	9.8	6.4	2.3	**-8.7**	**-10.8 to -6.5**
	P	371	31.3	12.9	18.9	21.6	15.4	373	48.0	13.1	16.9	15.0	7.0	**-14.9**	**-21.4 to -8.5**
Febrile neutropenia	C	2228	98.3	--	--	1.7	0.0	2110	99.3	--	--	0.7	0.0	**-0.9**	**-1.6 to -0.3**
	P	388	92.0	--	--	8.0	0.0	384	96.4	--	--	3.6	0.0	**-4.3**	**-7.6 to -1.1**
Supportive care: antibiotics[b]	C	1868	98.3	--	--	1.7	--	1768	97.9	--	--	2.1	--	0.4	-0.5 to 1.3
	P	383	93.2	--	--	6.8	--	370	90.5	--	--	9.5	--	2.7	-1.2 to 6.6
Supportive care: G-CSF[b]	C	1868	94.0	--	--	6.0	--	1767	98.2	--	--	1.8	--	-4.2	**-5.5 to -3.0**
	P	383	85.6	--	--	14.4	--	370	95.4	--	--	4.6	--	-9.8	**-13.9 to -5.7**

Source: du Bois et al, 2003.[17]

Abbreviations: --=not defined; C=maximum grade over all courses; CI=confidence interval; G-CSF=granulocyte colony-stimulating factor; E=estimate; N=number of courses in set C and number of patients in set P; NCI CTC=National Cancer Institute Common Toxicity Criteria;

Table 15-2 Hematologic Toxicities and Associated Supportive Care in Patients With Advanced Ovarian Cancer Stratified by Treatment Arm and Toxicity Grade

		NCI CTC Grade, %												Difference[a] in the Proportions of Patients With Grades 3/4 Toxicity, %	
		Paclitaxel/Carboplatin Arm						Cisplatin/Paclitaxel Arm							
Toxicity	**Set**	**N**	**0**	**1**	**2**	**3**	**4**	**N**	**0**	**1**	**2**	**3**	**4**	**E**	**95% CI**

P=maximum grade over all courses within a patient; pRBCs=packed red blood cells.

a Differences are calculated by subtracting the paclitaxel/carboplatin arm proportion from the cisplatin/paclitaxel arm proportion; statistically significant differences in proportions between the 2 treatment arms are in bold font. All percentages are rounded; therefore, the estimates may differ by ± 1 from the difference of the percentages of the treatment arm columns.

b Transfusion of pRBCs, use of antibiotics, and G-CSF were not assessed for the last treatment cycle within a patient. Use of antibiotics and G-CSF is graded in the same fashion as transfusion of pRBCs. Use of antibiotics/application of G-CSF is coded as a toxicity of Grade 3; a Grade 0 is applied otherwise.

15.2 Drugs Associated With Nephrotoxicity

The drugs listed in Table 15-3 are permitted to be used during the conduct of this study but should be used with caution.

Table 15-3 Drugs Associated with Nephrotoxicity

Analgesics	Cardiovascular agents
Nonsteroidal anti-inflammatory drugs	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers
Antidepressants/mood stabilizers	Clopidogrel (Plavix), ticlopidine (Ticlid)
Lithium	Contrast dye
Antimicrobials	Diuretics
Acyclovir (Zovirax)	Loops, thiazides
Aminoglycosides	Triamterene (Dyrenium)
Amphotericin B (Fungizone; deoxycholic acid formulation more so than the lipid formulation)	Herbals
Beta lactams (penicillins, cephalosporins)	Chinese herbals with aristocholic acid
Foscarnet (Foscavir)	Others
Ganciclovir (Cytovene)	Allopurinol (Zyloprim)
Pentamidine (Pentam)	Gold therapy
Quinolones	Haloperidol (Haldol)
Rifampin (Rifadin)	Pamidronate (Aredia)
Sulfonamides	Phenytoin (Dilantin)
Vancomycin (Vancocin)	Quinine (Qualaquin)
Antiretrovirals	Zoledronate (Zometa)
Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)	
Indinavir (Crixivan)	
Calcineurin inhibitors	
Cyclosporine (Neoral)	
Tacrolimus (Prograf)	

Source: Modified from Naughton et al, 2008.[18]

15.3 Response Criteria

Disease Response Criteria for Target and Nontarget Lesions

Evaluation of Target Lesions	
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
Evaluation of Nontarget Lesions	
CR	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
Non-CR/non-PD	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

Source: Eisenhauer et al, 2009.[14]

Overall Disease Response Criteria

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer et al, 2009.[14]
Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

15.4 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

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

Source: Oken et al, 1982.[19]

15.5 Formula for Absolute Neutrophil Count Calculation

ANC=total leukocyte count × total percentage of neutrophils (segmented neutrophils+band neutrophils)

Example

If: total leukocyte count=4.3; segmented neutrophils=48%; band neutrophils=2%

Then: 4300 × (0.48+0.02)=4300 × 0.5=ANC of 2150

15.6 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times \text{(serum creatinine [mg/dL])}} \text{ OR } \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{0.81 \times \text{(serum creatinine [µmol/L])}}$$

For females:

$$\text{Creatinine Clearance} = 0.85 \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times \text{(serum creatinine [mg/dL])}} \text{ OR } 0.85 \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times \text{(serum creatinine[µmol/L])}}$$

15.7 Excluded CYP3A Inducers

Note that HIV medications that are strong CYP3A inducers are not included in this list because HIV-positive patients are excluded from study participation.

Use of the clinically significant CYP3A inducers listed in Table 15-4 should be avoided during MLN4924 therapy.

Table 15-4 In Vivo Inducers of CYP3A

Strong Inducers **≥ 80% Decrease in AUC**	**Moderate Inducers** **50%-80% Decrease in AUC**
Carbamazepine	Bosentan
Phenytoin	Efavirenz
Phenobarbital	Modafinil
Primidone	Nafcillin
Rifabutin	
Rifampin	
Rifapentine	
St. John's Wort	

Abbreviations: AUC=area under the plasma concentration versus time curve; CYP=cytochrome P450.
This is not an exhaustive list; please refer to the following sources: medicine.iupui.edu/flockhart/table.htm and fda.gov/CDER/drug/drugInteractions/tableSubstrates.htm for additional information.

15.8 New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease.[20]

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

15.9 Classification of Chronic Obstructive Pulmonary Disease by Spirometry

Table 15-5 Classification of Chronic Obstructive Pulmonary Disease by Spirometry

Stage	Severity	FEV_1/FVC	FEV_1
Stage I	Mild	< 0.70	$FEV_1 \geq 80\%$ predicted
Stage II	Moderate	< 0.70	$50\% \leq FEV_1 < 80\%$ predicted
Stage III	Severe	< 0.70	$30\% \leq FEV_1 < 50\%$ predicted
Stage IV	Very severe	< 0.70	$FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

15.10 Methods of Contraception Considered to be Effective

Acceptable Contraception 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 to be highly effective. Such methods include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[a]:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - Oral.
  - Injectable.
  - Implantable.[b]
- Intrauterine device.[b]
- Intrauterine hormone-releasing system.[b]

- Bilateral tubal occlusion.[b]
- Vasectomised partner.[b,c]
- Sexual abstinence.[d]

Contraception Methods Considered Less Highly Effective

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

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

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[b] Contraception methods that in the context of this guidance are considered to have low user dependency.
[c] 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.
[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective birth control methods.

15.11 Amendment 1 Rationale and Purpose

Rationale for Amendment 1

The primary purpose of this amendment is to enroll additional patients in this study to further evaluate the effect of the strong cytochrome P450 (CYP) 3A inhibitor, itraconazole, on MLN4924 pharmacokinetics (PK) at the clinically relevant dose of MLN4924, 20 mg/m^2. On the basis of preliminary assessments from 26 patients (13 fluconazole, 13 itraconazole) who have completed Part A to date, steady-state exposures of fluconazole (classified as a moderate CYP3A inhibitor) had minimal effect (average 13% increase in area under the plasma concentration versus time curve from time zero to infinity) on the single-dose

intravenous (IV) PK of MLN4924, while MLN4924 systemic exposure increased by 23% on average in the presence of itraconazole (classified as a strong CYP3A inhibitor). These modest drug interaction effects observed with 2 validated moderate and strong CYP3A inhibitor probes, respectively, appear inconsistent with the currently available in vitro metabolism data indicating a major role of CYP3A in MLN4924 metabolism. The information from these additional patients will provide further understanding of the contribution of CYP3A metabolism to the disposition of MLN4924 in humans within the clinically relevant dose range in support of adequate labeling.

On the basis of the emerging safety information in the 26 patients, co-administration of MLN4924 with fluconazole or itraconazole was generally well tolerated. The proposed single IV dose of MLN4924, 20 mg/m^2, is approximately 5-fold lower than doses of MLN4924 equal to or above 110 mg/m^2, which were associated with more severe Cycle 1 Day 1 adverse events in phase 1 studies of MLN4924. Also, on the basis of the dose-linear PK of MLN4924 and observed 23% increase in MLN4924 systemic exposure by itraconazole at a single 8-mg/m^2 dose, it can be inferred that plasma exposures of MLN4924 when administered at a single 20-mg/m^2 dose with itraconazole can be expected to be well below exposures seen at doses $\geq$ 110 mg/m^2.

Before enrolling patients at the target dose of 20 mg/m^2 MLN4924, an intermediate dose of 15 mg/m^2 MLN4924+itraconazole will be evaluated as a safety lead-in cohort. If the review of safety and PK data from 3 PK-evaluable patients in this safety lead-in cohort confirms that the anticipated safety margin is adequate, enrollment into the 20-mg/m^2 MLN4924 arm will begin. Thus, this amendment is adding a total of approximately 20 patients to the Itraconazole Arm: approximately 4 patients (for 3 PK evaluable) in the safety lead-in cohort and approximately 16 patients (for 12 PK evaluable) in the 20-mg/m^2 MLN4924 cohort.

The 3-hours postdose vital sign assessment will no longer be required in Part B. This change is based on the available safety data from the MLN4924 program; at the doses to be explored in this study, there have been no significant alterations of vital signs reported at 3 hours postdose. Furthermore, the change is aligned with the current Study C15010 on which Part B of this study is based. Study C15010 does not require 3-hours postdose vital signs for the same safety considerations.

Dose modifications related to platelet counts have been clarified to ensure that MLN4924 dosing is delayed if the platelet count is < 100,000/µL during Cycle 2 and beyond.

Purposes for Amendment 1

The purposes of this amendment are as follows:

- Add 12 PK-evaluable patients to evaluate the CYP3A inhibition-mediated drug interaction effect of itraconazole on MLN4924 PK at the clinically relevant dose of 20 mg/m^2 MLN4924.
- Add 3 PK-evaluable patients treated with 15 mg/m^2 MLN4924 in the Itraconazole Arm as an intermediate safety lead-in step before dosing any patients with 20 mg/m^2 MLN4924.
- Update the stopping rules for the additional patients enrolled in the new Itraconazole Arm, 20-mg/m^2 MLN4924 Cohort, on the basis of review of the Part A safety and PK data obtained from the Safety Lead-in 15-mg/m^2 MLN4924 Cohort.

- Include the possibility that a subset of the PK samples may be used for measurement of concentration of the co-administered drugs (fluconazole or itraconazole), if considered necessary to verify treatment assignments.
- Remove vital signs measurement at 3 hours postdose in Part B (ie, Days 1, 3, and 5 of all cycles in Part B) for all patients.
- Clarify in Table 6-1 that the platelet count must be > 100,000/μL on ***any*** dosing day in Cycles ≥ 2, or MLN4924 dosing will be delayed and chemotherapy dose may be modified.
- Correct a typographical error in Inclusion Criterion 6 (the unit for creatinine clearance is now mL/minute, instead of L/minute as incorrectly stated in the original protocol).
- Revise text within Section 8.1, Statistical Methods: safety populations and treatment-emergent adverse events are defined separately for Part A and Part B, and details have been added for electrocardiogram and vital sign assessments.
- Correct typographical errors, punctuation, grammar, and formatting.

15.12 Amendment 2 Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 2 are indicated. The corresponding text has been revised throughout the protocol. All changes are applicable after completion of Cycle 12.

Change 1: Extend the 2-day window for scheduling issues (eg, inclement weather, holidays, vacations, or other administrative reasons) to 2 weeks; treatment breaks of up to 4 weeks may be permitted after discussion between the investigator and the project clinician or designee, and the investigator will confirm patient eligibility for continued treatment upon return, before treatment.

The primary change occurs in: Section 6.4.2 Dose Modification Guidelines for MLN4924:

Added text:	**For patients who take treatment breaks at the investigator's discretion, patient eligibility for continued treatment, including all Day 1 predose assessments specified in the Schedules of Events, will be confirmed by the investigator before resumption of treatment. Treatment breaks must be no longer than 2 weeks in duration (4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively.**

Rationale for Change:

The visit window for assessments was extended to 2 weeks to accommodate scheduling issues, and an option for treatment breaks (up to 4 weeks after consulting with the sponsor) was added to allow flexibility for patients continuing beyond 12 cycles of treatment.

The following sections also contain this change:

- Protocol Summary.
- Section 4.1 Overview of Study Design.
- Section 4.3 Duration of Study.
- Section 6.1.2 Continued Treatment With MLN4924 in Combination With Standard of Care (Part B).
- Section 7.4 Study Procedures.
- Section 7.8 Study Compliance.

Change 2: Reduce the frequency of disease response assessments from every 3 cycles to every 6 cycles.

The primary change occurs in Section 7.4.16 Disease Assessment (Part B):

Added text: Computed tomography scans with IV contrast encompassing the known sites of disease will also be performed at the end of Cycle 2, end of Cycle 4, and at the end of every other cycle **(Cycles 1-12), or after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 2)** thereafter. **Additional CT scans may be performed, per investigator's discretion, if clinically indicated.**

Rationale for Change:

The reduction in frequency of disease response assessments was made to lessen the burden for patients continuing beyond 12 cycles of treatment.

The following sections also contain this change:

- Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 13 and Beyond (as of Amendment 2).
- Section 4.1 Overview of Study Design.

Change 3: Reduce the frequency of hematology, vital sign, clinical chemistry, and electrocardiogram assessments and physical examinations.

The primary change is reflected in the new Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 13 and Beyond (as of Amendment 2):

Description of change: Day 8 hematology, vital signs, clinical chemistry, and symptom-directed physical examination are not present in the new Schedule of Events for Cycle 13 and Beyond. As these were the only activities on Day 8, the clinic visit on this day is not present in the new Schedule of Events. The complete physical examination on Day 1 was replaced with a symptom-directed physical examination.

Rationale for Change:

The Day 8 hematology assessment, vital signs assessment, clinical chemistry panel, and symptom-directed physical examination and the Day 1 complete physical examination are not present in the new Schedule of Events for Cycle 13 and beyond because these assessments are no longer considered necessary for patients continuing beyond 12 cycles of treatment; on Day 1, a symptom-directed physical examination was considered sufficient.

Change 4: Add phosphate to the urinalysis parameters.

The primary change is reflected in Section 7.4.15 Clinical Laboratory Evaluations:

Description of change: Phosphate has been added to the urinalysis parameters after completion of Cycle 12.

Rationale for Change:

Phosphate has been added to the urinalysis parameters to be consistent with program-wide recommendations.

Change 5: Add a ±10-minute window to the MLN4924 infusion duration.

The primary change occurs in Section 6.1.2 Continued Treatment With MLN4924 in Combination With Standard of Care (Part B):

Added text: Patients will receive MLN4924 **given as a 1-hour (±10 minutes as of Amendment 2) IV infusion** in combination with either docetaxel or with carboplatin+paclitaxel at a dose regimen informed from Study C15010 that has been deemed tolerable (eg, no DLTs in 3 patients or no more than 1 DLT in 6 patients).

Rationale for Change:

The addition of the ±10-minute window to the MLN4924 infusion duration was made to allow flexibility in MLN4924 infusion duration.

The following sections also contain this change:

- Study Flow Diagram 2.
- Section 4.1 Overview of Study Design.

Change 6: Remove the requirement for independent data monitoring committee monitoring.

The primary change occurs in deleted Section 9.2 Independent Data Monitoring Committee:

Deleted text:

~~9.2 Independent Data Monitoring Committee~~

~~An IDMC has been formed to periodically monitor the overall conduct of studies within the MLN4924 program, including review of accumulating clinical study data and safety data (both clinical and nonclinical) and to make recommendations to Millennium to safeguard the interests of study participants. Additionally, the IDMC may make recommendations relating to the selection/recruitment/ retention of study participants, patient management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. Further details regarding the IDMC are located in the IDMC charter.~~

Rationale for Change:

No new safety issues were identified from Study C15011 data analyzed during IDMC meetings, and only 3 patients remain active in the study; therefore, as of Amendment 2 implementation, the IDMC will no longer be required to monitor Study C15011.

Section 1.6.1 Risks of MLN4924 Therapy also contains this change.

Change 7: Adjust contraception requirements to be consistent with Clinical Trial Facilitation Group recommendations.

The primary change occurs in Section 6.7.1 MLN4924:

Initial wording:

6.7.1 MLN4924

…

- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form (ICF) through 4 months 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, and postovulation methods] and withdrawal are not acceptable methods of contraception.)

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

…

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

Amended or new wording:

6.7.1 MLN4924

…

- **As of Amendment 2,** ~~I~~if they are of childbearing potential, agree to practice ~~2~~ **1 highly** effective method~~s~~ **and 1 additional effective (barrier) method** of contraception**, at the same time,** from the time of signing the ICF through 4 months 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~~ **patient**. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], ~~and~~ withdrawal, **spermicides only [as of Amendment 2], and lactational amenorrhea [as of Amendment 2]** are not acceptable methods of contraception. **Female and male condoms should not be used together.**)

As of Amendment 2, female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

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

…

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the ~~subject~~ **patient**. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods for the female partner], ~~and~~ withdrawal, **spermicides only [as of Amendment 2], and lactational amenorrhea [as of Amendment 2]** are not acceptable methods of contraception. **Female and male condoms should not be used together.**)

As of Amendment 2, male patients must agree to not donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

Rationale for Change:

The update in contraception requirements was included for consistency with program-wide updates.

The following sections also contain this change:

- Section 5.1.Inclusion Criteria.
- Section 15.10 Methods of Contraception Considered to be Effective.

Change 8: Update the description of the drug product.

The primary change occurs in Section 6.11.1 MLN4924:

Initial wording:	The drug product is labeled MLN4924 (MLN4924-003 Injection).
Amended or new wording:	The drug product is labeled MLN4924 (MLN4924-003 ~~Injection~~ **concentrate for solution for infusion**).

Rationale for Change:

The update of drug product description was an administrative change in response to the new, program-wide description for the drug product.

The following sections also contain this change:

- Section 6.12.1 MLN4924.
- Section 6.13.1 MLN4924.
- Section 6.14.1 MLN4924.

Change 9: Update the investigator responsibilities for compliance with updated International Conference on Harmonisation guidelines.

The primary change occurs in Section 11.1 Good Clinical Practice:

Added Text:	**The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.**

Rationale for Change:

Investigator responsibilities were updated to comply with updated changes in ICH guidelines.

Change 10: Update the description of dose-limiting toxicities observed in Study C15003 to be consistent with final data.

The primary change occurs in Section 1.4 MLN4924 Clinical Experience:

Initial wording:	The maximum tolerated dose (MTD) for Schedule A was established at 59 mg/m^2 based on dose-limiting toxicities (DLTs) of increased transaminases and shock observed at a dose level of 79 mg/m^2.
Amended or new wording:	The maximum tolerated dose (MTD) for Schedule A was established at 59 mg/m^2 based on **a** dose-limiting toxicity~~ies~~ (DLT~~s~~) of increased transaminases ~~and shock~~ observed at a dose level of ~~79~~ **78** mg/m^2.

Rationale for Change:

The description of DLTs observed in Study C15003 were updated to be consistent with the final data presented in the Investigator's Brochure and clinical study report.

Change 11: Update vital signs assessments to allow measurements to be taken with the patient in the supine or sitting position.

The primary change occurs in Section 7.4.9 Vital Signs:

Added text: Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected as indicated in the Schedules of Events and as clinically indicated. All vital signs will be measured in the sitting position **(and/or supine after completion of Cycle 12)** as noted in the Schedules of Events.

Rationale for Change:

Supine vital signs assessments are permitted after completion of Cycle 12, consistent with program-wide recommendations.

The Schedule of Events for Continued Treatment With MLN4924+Standard of Care (Part B): Cycle 13 and Beyond (as of Amendment 2) also contains this change.

Change 12: Clarify the timing of transfusion for red blood cells to at least 1 day before study drug administration.

The primary change occurs in Section 6.6.2 Permitted Concomitant Medications and Procedures (Part B):

Added text: Red blood cell transfusions must be administered before administration of study drug **(ie, day before dosing)**. Each transfusion episode, including the type of transfusion (red blood cell), should be recorded.

Rationale for Change:

The timing of transfusions was revised to occur at least 1 day before study drug administration.

Section 6.9.2 Guidance for Clinical Assessment and Management of Anemia also contains this change.

Change 13: Remove gamma glutamyl transferase from the serum chemistry parameters.

The primary change occurs in Section 7.4.15 Clinical Laboratory Evaluations:

Description of Change: Assessment of gamma glutamyl transferase as part of serum chemistry is no longer required after completion of Cycle 12.

Rationale for Change:

Assessment of gamma glutamyl transferase is no longer considered necessary for patients continuing beyond 12 cycles of treatment.

Change 14: Remove known breast cancer resistance protein substrates, moderate and strong inhibitors of cytochrome P450 3A4, and inhibitors of P-glycoprotein from the list of excluded concomitant medications.

The primary change occurs in Section 6.5.2 Excluded Concomitant Medications and Procedures (Part B):

Description of Change	Known BCRP substrates, moderate and strong inhibitors of CYP3A4, and inhibitors of P-gp were removed from the list of excluded concomitant medications.

Rationale for Change:

Known BCRP substrates, moderate and strong inhibitors of CYP3A4, and inhibitors of P-gp are no longer prohibited for MLN4924 therapy. Preliminary data from 11 patients who completed protocol-specified dosing and PK evaluations to assess the effect of itraconazole, a strong CYP3A inhibitor and P-gp inhibitor, on pevonedistat PK indicated that systemic exposures of pevonedistat following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to those in the absence of itraconazole. The data support removing strong CYP3A inhibitors and P-gp inhibitors from the list of prohibited concomitant medications in ongoing and planned pevonedistat clinical studies. The rationale for removing substrates of BCRP from excluded concomitant medications is based on an assessment of the DDI potential of MLN4924. When viewed in the context of the MLN4924 mean C_{max} value observed at the established MTD of 20 mg/m^2 for the combination of MLN4924 plus azacitidine in Study C15009, MLN4924 is unlikely to inhibit the drug efflux transporter, and hence affect the PK of other drugs that are known BCRP substrates.

The following sections also contain this change:

- Section 5.2 Exclusion Criteria.
- Section 15.7 Excluded CYP3A Inducers.

Change 15: Replace references to the Safety Management Attachment with references to the Development Core Safety Information.

The primary change occurs in Section 1.6.1 Risks of MLN4924 Therapy:

Initial wording:	Additional information on risks is provided in the IB and the SMA.

Amended or new wording:	Additional information on risks is provided in the IB and the ~~SMA~~**DCSI.**

Rationale for Change:

The content of the Safety Management Attachment has been incorporated into the DCSI which renders the Safety Management Attachment obsolete.

The following sections also contain this change:

- Section 1.4 MLN4924 Clinical Experience.
- Section 6.9 Management of Clinical Events.

Change 16: Update the description of the Safety Management Team to be consistent with current preferred language and to reflect its cross-functional nature.

The primary change occurs in Section 9.1 Millennium Safety Assessments:

Initial wording:	Safety data will be reviewed and assessed periodically by an internal safety working group throughout the conduct of the study. These reviews will include a safety physician, a clinical physician from the study team, and other representation from the Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, Regulatory Affairs, Drug Safety Evaluation/Toxicology, and Clinical Operations departments at Millennium. Escalation of safety issues to a senior management cross-functional safety board will be performed on an ad hoc basis.
Amended or new wording:	Safety data will be reviewed and assessed periodically by ~~an internal safety working group~~ **a Global Pharmacovigilance team and a cross-functional Safety Management Team** throughout the conduct of the study. These **cross-functional** reviews will include a ~~safety physician, a clinical physician~~ **Global Safety Lead** from the study team, ~~and~~ **as well as** other representation from ~~the Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, Regulatory Affairs, Drug Safety Evaluation/Toxicology, and Clinical Operations~~ **other** departments at Millennium **such as Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, and Clinical Operations**. ~~Escalation of safety issues to a senior management cross-functional safety board will be performed on an ad hoc basis.~~

Rationale for Change:

This language was updated to be consistent with preferred terminology across the program and to reflect the cross-functional nature of the teams reviewing safety data.

Change 17: Update contact information for product complaints.

The primary change occurs in Section 11.11 Product Complaints:

Initial wording:

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 PPD (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,
PPD

Amended or new wording:

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~~ PPD ~~(see below) and report the event~~ **report this via the phone numbers or email address provided below**. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

PPD

Call Center	Phone Number	Email	Fax
PPD			

Rationale for Change:

This contact information was updated to reflect an administrative change.

Amendment 2 to A Phase 1 Study to Evaluate the Effects of Fluconazole and Itraconazole CYP3A–mediated Inhibition on the Pharmacokinetics, Safety and Tolerability of MLN4924 in Patients With Advanced Solid Tumors

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	19-Apr-2017 02:03 UTC
	Clinical Approval	19-Apr-2017 02:55 UTC
	Clinical Pharmacology Approval	19-Apr-2017 05:32 UTC