



Title: A Phase 1b Study of Alisertib (MLN8237) in Combination With Weekly Paclitaxel in East Asian Patients With Advanced Solid Tumors

NCT Number: NCT02367352

Protocol Approve Date: 01 June 2015

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

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

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

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**CLINICAL STUDY PROTOCOL C14022 AMENDMENT 01**

**Alisertib (MLN8237)**

***A Phase 1b Study of Alisertib (MLN8237) in Combination With Weekly Paclitaxel in East Asian Patients With Advanced Solid Tumors***

**Protocol Number:** C14022  
**Indication:** Advanced solid tumors (dose escalation)  
**Phase:** Ovarian cancer or small cell lung cancer (dose expansion)  
**Sponsor:** 1b  
**Therapeutic Area:** Millennium Pharmaceuticals, Inc.  
**Oncology**

**Protocol History**

Original 30 September 2014  
Amendment 01 01 June 2015

Millennium Pharmaceuticals, Inc.  
40 Landsdowne Street  
Cambridge, MA USA 02139  
Telephone: +1 (617) 679-7000

Approved by:

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

---

PPD  Signature Date DD Month YYYY

---

PPD  Signature Date DD Month YYYY

**Confidentiality Statement**

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

## **Rationale for Amendment 01**

The major purposes for this amendment are to add dose adjustment guidance for management of oral mucositis and to provide the updated dose interruption rule during a cycle. This amendment also includes other clarifications and corrections to address the feedback received from the health authority and for accuracy and consistency.

## **Purposes for Amendment 01**

The purposes of this amendment are to:

- Remove visit windows of  $\pm 2$  days from footnotes to remove repetition.
- Allow body temperature to be measured according to local practice at study time points other than at Screening and Cycle 1; all Screening and Cycle 1 measurements must be taken orally.
- Clarify the timing of CA-125 level assessments (for patients with ovarian cancer).
- Clarify the screening requirements for HBV and HCV, and to add details of monitoring for patients who test HBcAb+ at Screening.
- Adjust the requirement for disease evaluation so that patients will be evaluated up to progressive disease.
- Clarify that paclitaxel and alisertib should be administered 1 hour apart on Cycle 1, Day 1.
- Allow a longer window for adjusting dosing and study assessments due to safety concerns (+3 days, rather than +2 days, allowed for administrative reasons).
- Clarify the timing for the predose paclitaxel PK sample collection on Day 1.
- Correct errors in percents reported for adverse events in the pooled data from single-agent studies of alisertib.
- Allow for expansion of dose escalation cohort(s) to enable a better understanding of safety and/or PK, if needed.
- Clarify that there will be **approximately** 2 to 3 study centers in the escalation part of the study.
- Redefine adequate renal function (Inclusion Criterion 8) by either creatinine levels or estimated creatinine clearance.
- Add details to clarify Inclusion Criterion 9 regarding previous chemotherapy regimen allowance.
- Revise Exclusion Criterion 11 to specify that there must be no use of proton pump inhibitors within 5 days (rather than 4 days) of the first dose of alisertib.
- Revise Exclusion Criterion 19 to specify uncontrolled cardiac arrhythmias.
- Add an exclusion criterion (Exclusion Criterion 21) for patients with another malignancy within the past 3 years.
- Add details to the instructions for patients regarding the timing of study medication dosing, and add a statement that the study medication should be swallowed whole and not chewed.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

- Revise paclitaxel dosing instructions to specify that the length of paclitaxel infusion on Cycle 1, Day 1 and Cycle 2, Day 1 should be 60 minutes (it must not be less than 60 minutes, but may be up to 70 minutes maximum, where necessary), while paclitaxel should be infused over at least 1 hour (but not more than 90 minutes) at all other dosing time points.
- Allow prophylactic antiemetics during Cycle 1 and allow modifications to premedications without the requirement for project clinician approval.
- Clarify that thrombocytopenia with clinically significant bleeding is a DLT if it is **greater than or equal to** Grade 3 in the dose-limiting toxicity definitions.
- Clarify actions at Dose Level 3 (20-mg BID alisertib).
- Specify that PK exposure data will be used to support the determination of the recommended phase 2 dose (RP2D).
- Extend the minimum rest period between cycles from 10 days to at least 11 days and a maximum of 21 days.
- Revise the criteria for dose interruption during a cycle.
- Revise the dose modification instructions for dose-limiting hematologic toxicities.
- Add specific dose adjustment requirements due to occurrence of oral mucositis/stomatitis/mouth ulcers.
- Clarify that alternative therapy or medicine(s) are not allowed.
- Prohibit the use of pancreatic enzyme during the study.
- Permit premedication with corticosteroids, diphenhydramine, or histamine-2 receptor antagonists before each treatment with paclitaxel.
- Correct the definition of women of childbearing potential.
- Clarify that radiographic images will be provided to the sponsor **if necessary**.
- Clarify when patients who are withdrawn in Cycle 1 should be replaced.
- Add clarification to DLT-evaluable population.
- Update the TEAE definition to the current template.
- Remove final study analysis description from interim analysis section.
- Remove administrative language regarding study closure that was intended for a European regulatory system and is not applicable to this study.
- Correct typographical errors, punctuation, grammar, and formatting.

For specific examples of changes in text and where the changes are located, see Section [14.5](#).

## PROTOCOL SUMMARY

**Study Title:** A Phase 1b Study of Alisertib (MLN8237) in Combination With Weekly Paclitaxel in East Asian Patients With Advanced Solid Tumors

**Number of Patients:** Approximately 30 patients will be enrolled in this study, including a minimum of 12 patients with epithelial ovarian cancer (OC) and small cell lung cancer (SCLC) (combined) in the expansion cohort.

### Study Objectives

#### Primary

- To evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) to subsequently define a recommended phase 2 dose (RP2D) of alisertib in combination with weekly paclitaxel in East Asian patients with advanced solid tumors
- To characterize the pharmacokinetics (PK) of alisertib and paclitaxel in the combination setting in East Asian patients with advanced solid tumors

#### Secondary (For Expansion Only)

- To identify initial signs of antitumor activity in patients with relapsed/refractory OC or SCLC

**Overview of Study Design:** This is an open-label, multicenter, phase 1b study to evaluate the safety, tolerability, and PK of alisertib in combination with weekly paclitaxel in East Asian patients. The study is in 2 parts: the first part is a dose escalation to determine the MTD and define the RP2D of the alisertib plus paclitaxel combination in East Asian patients with advanced solid tumors; the second part is an expansion cohort at the RP2D of the alisertib plus paclitaxel combination in East Asian patients with either OC or SCLC.

Alisertib will be administered orally 3 days on/4 days off for 3 weeks on Days 1 through 3, 8 through 10, and 15 through 17 in 28-day cycles. Paclitaxel 60 mg/m<sup>2</sup> IV will be administered on Days 1, 8, and 15 in 28-day cycles. The paclitaxel dose will remain constant throughout the dose escalation and expansion parts of this study.

Enrolled patients may receive study drug until observed progression, need of discontinuation because of toxicity, lost to follow-up, study is terminated by the sponsor, protocol violation, unsatisfactory therapeutic response, or voluntary withdrawal by the patient from the study. Patients may discontinue therapy at any time. Patients will attend the End of Treatment visit 30 days after receiving their last dose of study drug.

A dose escalation (3 + 3 schema) will be used to determine the MTD and the RP2D of the combination (as detailed in Section 6.4), which will be further evaluated in the expansion part of the study. The starting dose will be 15 mg BID alisertib (dose level [DL] 1); the next planned dose level is 25 mg BID alisertib (DL2). If  $\geq 2$  patients experience a DLT at 25 mg, alisertib will be de-escalated, and an intermediate dose level of alisertib 20 mg BID (DL3-intermediate) will be explored. The MTD/RP2D will require first-cycle DLTs in not more than 1 in 6 DLT-evaluable patients enrolled in a given dose level. If  $\geq 2$  of the first 6 patients experience a DLT at DL1, depending on the overall safety profile, the type of

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

AEs/DLTs observed, and the available PK data, a decision will be made either to expand the 15 mg BID alisertib (DL1) cohort with 6 additional patients, or to de-escalate the alisertib dose to 10 mg BID (DL-1), or to terminate the study. In the case of an expansion of the DL1 cohort, a tolerable dose will then require first-cycle DLTs in no more than 3 of 12 DLT-evaluable patients to confirm the MTD. If alisertib exposures in the combination setting in the East Asian population are unexpectedly lower than anticipated from single-agent experience in East Asian patients, and no DLTs have occurred in the DL2 cohort (alisertib 25 mg BID plus 60 mg/m<sup>2</sup> paclitaxel), the alisertib dose may be escalated further following discussion between the investigator and the sponsor pending PK and safety assessment. Should more data be needed to better understand the observed safety and/or PK, with the agreement of the sponsor's project clinician (or designee), cohort(s) at any dose level may be expanded. Intrapatient dose escalation will not be permitted in this study. It is planned that at least 1 Japanese patient will be included in each of the dose levels explored.

The effect of concomitant administration of alisertib on paclitaxel PK will be evaluated in this study. To this effect, alisertib doses will be held on Days 1 through 3 in Cycle 2 so that paclitaxel PK can be evaluated, in the absence of alisertib, following paclitaxel dose administration on Cycle 2, Day 1. Paclitaxel PK data on Cycle 2, Day 1 will serve as a reference for comparison with paclitaxel PK, evaluated at Cycle 1, Day 1 in the presence of alisertib. During the dose escalation and expansion part, for Cycle 2 only, patients will receive 12 doses of alisertib, administered BID on Days 8 through 10 and 15 through 17. The effect of alisertib on paclitaxel PK will be assessed in a minimum of 12 patients (inclusive of the expansion part) who complete protocol-specified dosing and PK measurements in the first 2 treatment cycles at the RP2D of the combination. Blood draws will be taken as detailed in the [Schedule of Events](#) and Section [7.4.17](#).

Pharmacokinetics of alisertib will be evaluated on Days 1 and 3 in Cycle 1 for both the dose escalation and expansion parts of the study. Blood draws will be taken as detailed in the [Schedule of Events](#) and Section [7.4.17](#).

An MTD should be established and then an RP2D will be defined based on all relevant considerations/parameters (eg, safety, tolerability, and PK).

After dose escalation has completed, patients with relapsed/refractory OC or SCLC will be enrolled into the dose expansion part of the study. During dose expansion, safety, tolerability, and initial signs of activity at the RP2D will be evaluated.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010.<sup>(1)</sup> Dose-limiting toxicities are defined in Section [6.3](#).

Adverse events will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of alisertib in combination with paclitaxel.

Patients cannot have received antineoplastic therapy or radiotherapy within the 21 days before enrollment (14 days for regimens with recovery expected within 7-14 days).

For all patients, scans (ie, CT and/or MRI) will be read locally. The investigator-assessed CR + PR (based on RECIST 1.1 criteria) will be used for efficacy assessment.

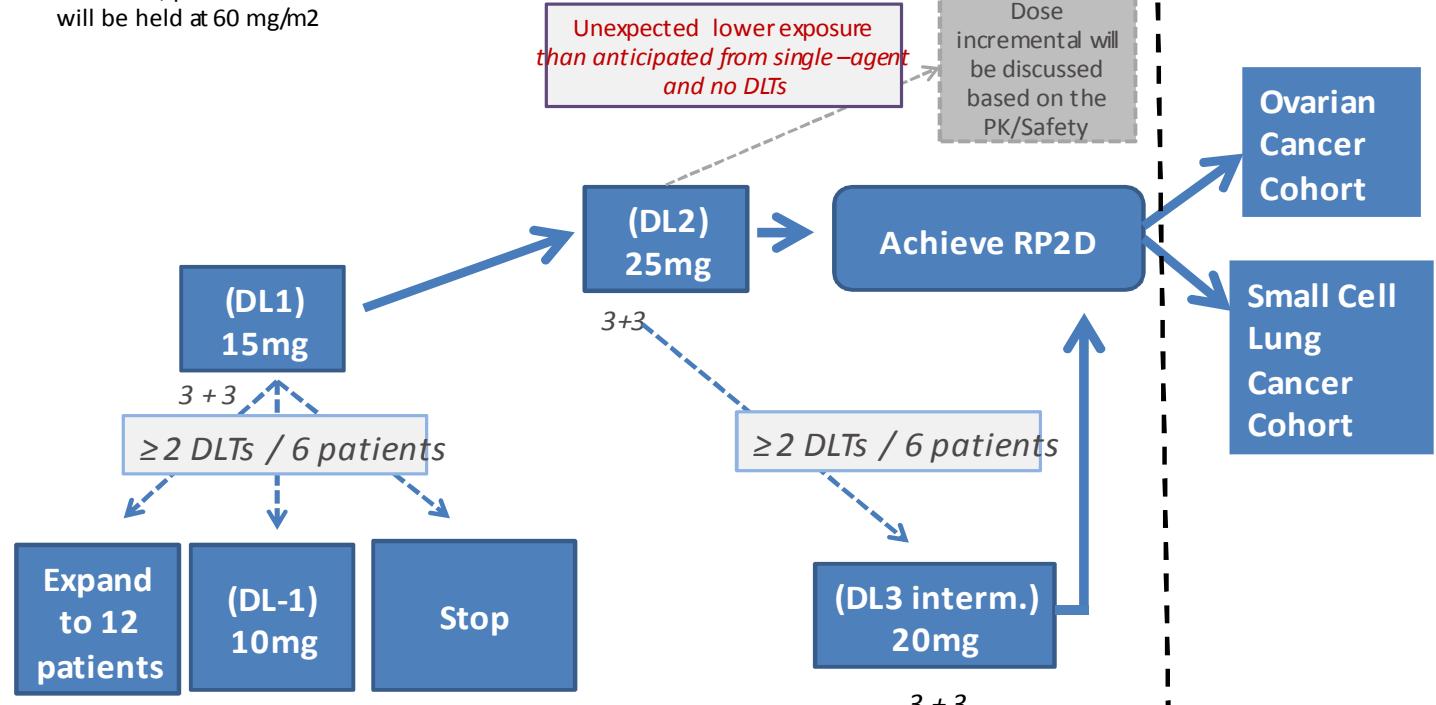
**Study Population:** The study population will consist of male or female East Asian patients aged 18 years or older who have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate hepatic, renal, and hematologic function; and who have been treated with no more than 2 previous chemotherapy regimens in the metastatic setting. Patients in the dose escalation part will have advanced solid tumors. Patients in the expansion part will have relapsed/refractory ovarian cancer or small cell lung cancer with measurable disease. Patients in the expansion part must not have received more than 2 prior taxane-containing regimens.

**Duration of Study:** It is anticipated that this study will last for approximately 24 months. The study will be closed once all the enrolled patients in the expansion part complete or discontinue from the study.

## STUDY OVERVIEW DIAGRAM

### Escalation Phase

Alisertib dose will be escalated, paclitaxel dose will be held at 60 mg/m<sup>2</sup>



Abbreviations: DL = dose level; DLT = dose limiting toxicity; RP2D = recommended phase 2 dose; PK = pharmacokinetic

## SCHEDULE OF EVENTS

Escalation (Patients With Advanced Solid Tumors) and Expansion (Patients With Relapsed/Refractory OC or SCLC)														
Procedure	Screen <sup>a</sup>	Cycle 1 (28-Day Cycle)							Subsequent 28-Day Cycles					EOT <sup>d</sup>
		Day							Day					
		1 <sup>b</sup>	2	3	8	9	10	15	21	1	2	3	8	15
Informed consent <sup>e</sup>	X													
Inclusion/Exclusion <sup>a</sup>	X													
Demographics	X													
Complete medical history <sup>f</sup>	X													
Complete physical examination with neurological examination	X													
Symptom-directed physical examination <sup>g</sup>		X <sup>b</sup>			X			X	X	X		X	X	X <sup>c</sup>
Vital signs <sup>h</sup>	X	X <sup>b</sup>			X			X	X	X		X	X	X <sup>c</sup>
Height	X													
Weight <sup>i</sup>	X	X <sup>b</sup>								X				X
ECOG performance status <sup>j</sup>	X	X <sup>b</sup>								X				X
Electrocardiogram <sup>k</sup>	X	X <sup>b</sup>												
Hematology <sup>l</sup>	X	X <sup>b</sup>			X			X	X	X		X	X	X <sup>c</sup>
Serum chemistry and TSH <sup>m</sup>	X	X <sup>b</sup>								X				X
Urinalysis <sup>n</sup>	X	X <sup>b</sup>												X
Serum pregnancy test <sup>o</sup>	X	X <sup>o</sup>												
CA-125 <sup>p</sup>	X	X							X					X
HBV and HCV testing <sup>q</sup>	X	HBV DNA should be monitored every 2 months if HBcAb is identified at Screening												
Extent of disease evaluation by RECIST, version 1.1 <sup>r</sup>	X												X <sup>r</sup>	X

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

Escalation (Patients With Advanced Solid Tumors) and Expansion (Patients With Relapsed/Refractory OC or SCLC)																	
Procedure	Screen <sup>a</sup>	Cycle 1 (28-Day Cycle)							Subsequent 28-Day Cycles							EOT <sup>d</sup>	
		Day							Day								
		1 <sup>b</sup>	2	3	8	9	10	15	21	1	2	3	8	15	21 <sup>c</sup>		
Concomitant medications and procedures		Recorded from 28-days before the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first															
Adverse event reporting		Recorded from the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first															
		<b>Serious adverse events</b> will be reported from signing of the informed consent form through 30 days after the last dose of study drug (see Section 9) <sup>s</sup>															
Paclitaxel PK samples <sup>t</sup>		X	X	X						In Cycle 2 only							
Alisertib PK samples <sup>u</sup>		X		X													
Administration of weekly paclitaxel <sup>v</sup>		X			X			X		X			X	X			
Administration of alisertib <sup>w</sup>		Days 1–3, 8–10, 15–17							Cycle 2 only: Days 8–10, 15–17 (no dosing on Days 1–3) Cycle 3 and beyond: same as Cycle 1 dosing								

Abbreviations:  $\beta$ -hCG = beta-human chionic gonadotropin; CXDY = Cycle X, Day Y; D = day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOS = End of Study visit; EOT = End of Treatment visit; FU = Follow-up; h = hour(s); min = minute(s); PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone.

Each treatment cycle is 28-days in length. Tests and procedures should be done on schedule, but visit windows of  $\pm$  2 days are allowed (except as otherwise specified) occasionally for holidays, vacations, and other administrative reasons. A dosing windows of  $\pm$  3 days is allowed due to safety concerns. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled assessment within this time frame, the patient may continue in the study only with written permission of the project clinician.**

- a Within 28-days before the Cycle 1, Day 1 dose of study drug, unless otherwise specified.
- b Cycle 1, Day 1 is baseline. Cycle 1, Day 1 evaluations and procedures are to be performed within the 4 days before the first dose of any study drug, unless otherwise specified. A repeat of the procedure is not required on Cycle 1, Day 1 if screening procedures were performed within 4 days of the Cycle 1, Day 1 dose of study drug. The exception is the CA-125, as 2 CA-125 values are required to be collected before dosing on Cycle 1, Day 1.
- c In patients who tolerate study treatment through multiple cycles, the Day 21 evaluation can be done by telephone contact, with or without laboratory testing and vital signs, at the discretion of the investigator, if in the prior 2 cycles the patient tolerated study treatment (ie, without the requirement for dose reduction or without  $\geq$  Grade 3 treatment-related toxicity evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI]

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

Escalation (Patients With Advanced Solid Tumors) and Expansion (Patients With Relapsed/Refractory OC or SCLC)																	
Procedure	Screen <sup>a</sup>	Cycle 1 (28-Day Cycle)								Subsequent 28-Day Cycles						EOT <sup>d</sup>	
		Day								Day							
		1 <sup>b</sup>	2	3	8	9	10	15	21	1	2	3	8	15	21 <sup>c</sup>		

CTCAE], version 4.03).

- d For all patients, the EOT visit will be conducted 30 (+ 10) days after the last dose of study drug for all patients.
- e Informed consent may be obtained earlier and must be obtained before performance of any study-specific procedures.
- f Including history of prior treatment for cancer.
- g The Cycle 1, Day 1 (baseline) symptom-directed physical examination is not required if the screening complete physical examination was conducted within the 4 days before administration of the Cycle 1, Day 1 dose of study drug. A symptom-directed physical examination will be repeated within 3 days before the beginning (Day 1) of each new treatment cycle; on Day 8, Day 15, and Day 21 of each treatment cycle; and at the EOT visit.
- h Vital signs (blood pressure, heart rate, and temperature) measurements will be obtained during screening; at Cycle 1, Day 1 (baseline); within 3 days before the beginning (Day 1) of each treatment cycle; on Day 8, Day 15, and Day 21; and at the EOT visit. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. If the screening assessment was done within 4 days before Cycle 1, Day 1, an assessment at Cycle 1, Day 1 is not necessary. During Screening and Cycle 1, temperature should be oral measurements only; temperature measurements in all other cycles may be taken based on local practice.
- i Weight will be measured at screening; at Cycle 1, Day 1 (baseline); within 3 days before the beginning (Day 1) of each treatment cycle; and at the EOT visit. If the screening assessment was done within 4 days before Cycle 1, Day 1, an assessment at Cycle 1, Day 1 is not necessary.
- j ECOG performance status will be assessed during screening; at Cycle 1, Day 1 (baseline); within 3 days before the beginning (Day 1) of each treatment cycle; and at the EOT visit. Refer to Section 14.1. If the screening assessment was done within 4 days before Cycle 1, Day 1, an assessment at Cycle 1, Day 1 is not necessary.
- k A 12-lead electrocardiogram (ECG) will be obtained at screening and at Cycle 1, Day 1 (baseline). If the screening ECG was obtained within the 4 days before the Cycle 1, Day 1 dose of study drug, a repeat ECG at Cycle 1, Day 1 is not necessary. Additional ECGs may be obtained if clinically indicated. Electrocardiogram assessments are to be performed with the patient supine and rested for 5 minutes and before any closely timed blood collection.
- l A blood sample for hematology will be obtained during screening; at Cycle 1, Day 1 (baseline); within 3 days before the beginning (Day 1) of each treatment cycle; on Day 8 (- 2 days), Day 15 (- 2 days), and Day 21 (- 2 days); and at the EOT visit. In patients who tolerate study treatment through multiple cycles, the Day 21 clinical laboratory assessment can become optional, at the discretion of the investigator, if in the prior 2 cycles the patient tolerated study treatment (ie, without the requirement for dose reduction or without  $\geq$  Grade 3 treatment-related toxicity evaluated according to NCI CTCAE, version 4.03). If screening values were obtained within the 4 days before Cycle 1, Day 1, repeat hematology testing at Cycle 1, Day 1 is not necessary. If a patient has an absolute neutrophil count (ANC) less than 500/mm<sup>3</sup> or a platelet count less than 25,000/mm<sup>3</sup>, or both, the complete blood count (CBC) with differential should be repeated at least every 2 to 3 days until the ANC or platelet count (or both, if both were decreased) have exceeded these values on at least 2 occasions.
- m A blood sample for serum chemistries will be obtained during screening; at Cycle 1, Day 1 (baseline); within 3 days before the beginning (Day 1) of each treatment cycle; and at the EOT visit. Thyroid stimulating hormone (TSH) level will be measured at screening or Cycle 1, Day 1 (baseline) and at the EOT visit; this test should be repeated during the treatment period as clinically indicated. If screening values were obtained and acceptable within the 4 days

Escalation (Patients With Advanced Solid Tumors) and Expansion (Patients With Relapsed/Refractory OC or SCLC)															
Procedure	Screen <sup>a</sup>	Cycle 1 (28-Day Cycle)							Subsequent 28-Day Cycles						EOT <sup>d</sup>
		Day							Day						
		1 <sup>b</sup>	2	3	8	9	10	15	21	1	2	3	8	15	21 <sup>c</sup>

before Cycle 1, Day 1, repeat clinical chemistry testing at Cycle 1, Day 1 is not necessary.

- n A urine sample for urinalysis will be obtained during screening, at Cycle 1, Day 1 (baseline), and at the EOT visit. If urine protein by dipstick changes to 3+ (or 2+ that is reconfirmed at least 1 day later), then a 24-hour urine collection should be done for protein and creatinine clearance. The screening or Cycle 1, Day 1 (baseline) urinalysis should include microscopic examination of the sediment. If screening values were obtained and acceptable within the 4 days before the Cycle 1, Day 1 dose of study drug, a repeat urinalysis at Cycle 1, Day 1 is not necessary.
- o A serum β-hCG pregnancy test will be performed only for patients of childbearing potential during screening and again at Cycle 1, Day 1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of any study drug (alisertib or paclitaxel) is administered (ie, within the 4 days before Cycle 1, Day 1), or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, as per request of IEC/IRB, or if required by local regulations.
- p For OC patients, CA-125 levels will be obtained according to standard of care within 9 days of screening and sufficient time after prior therapy, or during screening period; and within 4 days prior to the dose at Cycle 1, Day 1; and at the end of every treatment cycle, within the week prior to the start of new treatment cycle; and at the EOT visit. The investigator's determination of response by CA-125 is required at the end of every 2 cycles.
- q HBV and HCV screening must be conducted during the Screening period. HBV screening will include testing for hepatitis B surface antigen and hepatitis B core antibody (HBcAb). For patients who test positive for HBcAb, HBV DNA will also be assessed at screening. HCV screening will include testing for the anti-HCV antibody (HCVAb). Patients who test positive for HCVAb will also be tested for HCV-RNA at screening. Patients who are HBcAb positive at the screening will be monitored by assessment of DNA titers every 2 months.
- r Patients will undergo an evaluation of their disease with standard clinical examinations (eg, CT/MRI) to determine the extent of disease evaluation by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (see Section 7.4.15). Magnetic resonance imaging (MRI) scans may be used to assess sites of disease not adequately imaged by CT. If the patient has had appropriate scans performed within 28-days before the Cycle 1, Day 1 dose of alisertib, then those scans may be used for tumor lesion measurement during screening. Repeat CT (with IV contrast) or MRI scans, or both, are to be performed at the completion of Cycle 2 and at the completion of every 2 cycles (approximately every 8 weeks, between Days 21 and 28 of every even cycle) thereafter until PD is documented (except as permitted per agreement with the investigator and project clinician; see Section 7.4.15). The same imaging modality should be used throughout the study for each site of disease. For responders, radiographic images will be read locally but will be collected and, if necessary, will be provided to the sponsor for subsequent review. Scans are required at the EOT visit only if PD has not been documented previously and it has been 8 weeks or more since the previous evaluation. Other procedures, such as physical examinations and other scintigraphic examinations (eg, bone scans for patients with known or suspected bone metastases) should be taken into consideration also when evaluating the extent of malignant disease.
- s Only those serious events that occur after the first dose of any study drug will be entered in the eCRF, **although all serious adverse events and serious pretreatment events must be reported to the Millennium Department of Pharmacovigilance or designee.**
- t Blood samples to measure plasma concentrations of paclitaxel will be collected at the following time points on Day 1 of both Cycles 1 and 2: within 1 h before the start of the paclitaxel infusion; at the end of the paclitaxel infusion (immediately before switching off the infusion pump); at 5 (± 1) min, 15 (± 3) min, 0.5 h (± 5 min), 1 h (± 10 min), 2 h (± 20 min), 3 h (± 20 min), 7 h (± 30 min), 10 h (± 30 min), 23 (± 2) h, and 47 (± 4) h after completion of the

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

Escalation (Patients With Advanced Solid Tumors) and Expansion (Patients With Relapsed/Refractory OC or SCLC)																	
Procedure	Screen <sup>a</sup>	Cycle 1 (28-Day Cycle)							Subsequent 28-Day Cycles							EOT <sup>d</sup>	
		Day							Day								
		1 <sup>b</sup>	2	3	8	9	10	15	21	1	2	3	8	15	21 <sup>c</sup>		

paclitaxel infusion. The 23- and 47-h blood samples will be collected before alisertib dosing (see Section 7.4.17.1 and the [Alisertib and Paclitaxel PK Sampling Schedule](#)).

- u Blood samples to measure plasma concentrations of alisertib will be collected at the following time points on Days 1 and 3 in Cycle 1: immediately before the morning dose of alisertib, and at 1 h ( $\pm$  10 min), 2 h ( $\pm$  20 min), 3 h ( $\pm$  20 min), 4 h ( $\pm$  20 min), 5 h ( $\pm$  20 min), 9 h ( $\pm$  30 min), and 12 ( $\pm$  1) h after the alisertib morning dose on Days 1 and 3. (See Section 7.4.17.2 and [Alisertib and Paclitaxel PK Sampling Schedule](#))
- v Paclitaxel will be administered as a 1-hour intravenous (IV) infusion on Days 1, 8, and 15 of each 28-day treatment cycle (Section 6.2.1). Premedication may be administered in accordance with the recommendations described in the product label.
- w During Cycle 1, and Cycle 3 and beyond, alisertib dosing will begin on Day 1; subsequent dosing will occur on Days 2, 3, 8, 9, 10, 15, 16, and 17. During **Cycle 2 only**, alisertib dosing will begin on Day 8 and will continue on Days 9 and 10, and on Days 15, 16, and 17. Refer to [Table 6-1](#) for alisertib dose administration and titration schema. On Cycle 1 Day 1 when both paclitaxel and alisertib are administered, alisertib should be administered 1 hour before the start of the paclitaxel infusion. Alisertib will be dispensed to the patient on Day 1. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessment is completed before dosing. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the sponsor/designee clinician

**ALISERTIB AND PACLITAXEL PK SAMPLING SCHEDULE**

Day	Dosing		Paclitaxel PK (Cycle 1 and Cycle 2)		Alisertib PK (Cycle 1)	
	Alisertib	Paclitaxel	Timepoint	Sample	Timepoint	Sample
1	X		Predose	X <sup>a</sup>	Predose	X <sup>b,g</sup>
			X (start)		1 h (± 10 min)	X <sup>d</sup>
			X (end) <sup>c</sup>	End of infusion	X <sup>e</sup>	X <sup>d</sup>
			5 (± 1) min	X <sup>f</sup>		
			15 (± 3) min	X <sup>f</sup>		
			0.5 h (± 5 min)	X <sup>f</sup>		
			1 h (± 10 min)	X <sup>f</sup>	3 h (± 20 min)	X <sup>d</sup>
			2 h (± 20 min)	X <sup>f</sup>	4 h (± 20 min)	X <sup>d</sup>
			3 h (± 20 min)	X <sup>f</sup>	5 h (± 20 min)	X <sup>d</sup>
			7 h (± 30 min)	X <sup>f</sup>	9 h (± 30 min)	X <sup>d</sup>
			10 h (± 30 min)	X <sup>f</sup>	12 (± 1) h	X <sup>d</sup>
2	X		23 (± 2) h	X <sup>f</sup>		
3	X		47 (± 4) h	X <sup>f</sup>	Predose	X <sup>b,g</sup>
					1 h (± 10 min)	X <sup>d</sup>
					2 h (± 20 min)	X <sup>d</sup>
					3 h (± 20 min)	X <sup>d</sup>
					4 h (± 20 min)	X <sup>d</sup>
					5 h (± 20 min)	X <sup>d</sup>
					9 h (± 30 min)	X <sup>d</sup>
					12 (± 1) h	X <sup>d</sup>

Abbreviations: h = hour(s); min = minute(s); PK = pharmacokinetics.

a Within 1 h before the start of the paclitaxel infusion.

b Immediately before the morning dose of alisertib. On the day when both paclitaxel and alisertib are administered, alisertib should be administered 1 h before the start of the paclitaxel infusion.

c Paclitaxel should be infused over 60 (+ 10) minutes (Section 6.2.1).

d After the morning dose of alisertib.

e Immediately before switching off the infusion pump.

f After the completion of the paclitaxel infusion (ie, from the time the infusion pump is switched off).

g The predose sample for alisertib PK on Days 1 and 3 can be timed to coincide with the predose sample for paclitaxel PK on Day 1 and the 47-h paclitaxel PK sample depending on the timing of alisertib dosing.

## TABLE OF CONTENTS

LIST OF TABLES .....	16
LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS .....	17
1. BACKGROUND AND STUDY RATIONALE.....	20
1.1 Scientific Background .....	20
1.1.1 Study Drug .....	20
1.2 Nonclinical Experience.....	20
1.2.1 In Vitro Pharmacology.....	20
1.2.2 In Vivo Pharmacology .....	20
1.2.3 Safety Pharmacology and Toxicology.....	21
1.3 Clinical Experience .....	22
1.4 Disease Under Treatment.....	24
1.4.1 Epithelial Ovarian Cancer Epidemiology and Treatment .....	24
1.4.2 Small Cell Lung Cancer .....	25
1.5 Study Rationale .....	25
1.6 Dose Rationale .....	26
1.7 Potential Risks and Benefits .....	27
2. STUDY OBJECTIVES .....	28
2.1 Primary Objectives .....	28
2.2 Secondary Objective (For Expansion Only) .....	29
3. STUDY ENDPOINTS.....	29
3.1 Primary Endpoints .....	29
3.2 Secondary Endpoint.....	29
4. STUDY DESIGN.....	30
4.1 Overview of Study Design.....	30
4.2 Number of Patients .....	32
4.3 Duration of Study .....	32
5. STUDY POPULATION.....	33
5.1 Inclusion Criteria .....	33
5.2 Exclusion Criteria.....	35
6. STUDY DRUG .....	37
6.1 Study Drug Administration.....	37
6.2 Reference/Control Therapy .....	38
6.2.1 Paclitaxel .....	38
6.2.2 Premedication for Paclitaxel-Associated Hypersensitivity or Other Acute Reactions .....	38
6.3 Definitions of Dose-Limiting Toxicity.....	39
6.4 Dose Escalation Rules .....	40
6.5 Dose-Modification Guidelines .....	42
6.5.1 Criteria for Beginning a Subsequent Treatment Cycle .....	42
6.5.2 Criteria for Dose Interruption During a Cycle .....	43
6.5.3 Dose Modifications.....	44
6.6 Excluded Concomitant Medications and Procedures .....	48
6.7 Permitted Concomitant Medications and Procedures.....	49
6.8 Precautions and Restrictions .....	50

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

6.9 Management of Clinical Events .....	51
6.9.1 Nausea and Vomiting.....	51
6.9.2 Diarrhea.....	52
6.9.3 Central Nervous System Effects.....	52
6.9.4 Hypersensitivity Reactions Associated With Paclitaxel .....	52
6.10 Blinding and Unblinding .....	52
6.11 Description of Investigational Agents .....	52
6.12 Preparation, Reconstitution, and Dispensation .....	53
6.13 Packaging and Labeling.....	53
6.14 Storage, Handling, and Accountability.....	53
6.15 Other Protocol-Specified Materials .....	54
7. STUDY CONDUCT .....	54
7.1 Study Personnel and Organizations.....	54
7.2 Arrangements for Recruitment of Patients .....	55
7.3 Treatment Group Assignments .....	55
7.4 Study Procedures.....	55
7.4.1 Informed Consent .....	55
7.4.2 Patient Demographics .....	55
7.4.3 Medical History .....	55
7.4.4 Physical Examination.....	55
7.4.5 Patient Height and Weight .....	56
7.4.6 Vital Signs .....	56
7.4.7 Pregnancy Test .....	57
7.4.8 Concomitant Medications and Procedures.....	58
7.4.9 Adverse Events .....	58
7.4.10 Enrollment .....	58
7.4.11 Electrocardiogram.....	58
7.4.12 Clinical Laboratory Evaluations .....	58
7.4.13 CA-125 Assessment.....	60
7.4.14 HBV and HCV Assessment.....	60
7.4.15 Disease Assessment .....	61
7.4.16 Tumor Biopsies (Not Applicable).....	62
7.4.17 Pharmacokinetic Measurements .....	62
7.4.18 Pharmacodynamic Measurements (Not Applicable) .....	62
7.5 Completion of Treatment.....	62
7.6 Completion of Study.....	63
7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement.....	63
7.8 Withdrawal of Patients From Study .....	64
7.9 Study Compliance .....	65
8. STATISTICAL AND QUANTITATIVE ANALYSES .....	65
8.1 Statistical Methods .....	65
8.1.1 Determination of Sample Size .....	66
8.1.2 Randomization and Stratification .....	66
8.1.3 Populations for Analysis .....	66
8.1.4 Procedures for Handling Missing, Unused, and Spurious Data .....	66
8.1.5 Demographic and Baseline Characteristics .....	66

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

8.1.6 Efficacy Analysis .....	67
8.1.7 Pharmacokinetics/Pharmacodynamics/Biomarkers .....	67
8.1.8 Safety Analysis .....	68
8.1.9 Interim Analysis .....	69
9. ADVERSE EVENTS .....	69
9.1 Definitions .....	69
9.1.1 Pretreatment Event Definition .....	69
9.1.2 Adverse Event Definition .....	69
9.1.3 Serious Adverse Event Definition .....	70
9.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events .....	71
9.3 Monitoring of Adverse Events and Period of Observation .....	72
9.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events .....	72
10. ADMINISTRATIVE REQUIREMENTS .....	73
10.1 Good Clinical Practice .....	73
10.2 Data Quality Assurance .....	73
10.3 Electronic Case Report Form Completion .....	73
10.4 Study Monitoring .....	74
10.5 Ethical Considerations .....	74
10.6 Patient Information and Informed Consent .....	75
10.7 Patient Confidentiality .....	75
10.8 Investigator Compliance .....	75
10.9 On-site Audits .....	75
10.10 Investigator and Site Responsibility for Drug Accountability .....	76
10.11 Product Complaints .....	76
10.12 Closure of the Study .....	76
10.13 Record Retention .....	77
11. USE OF INFORMATION .....	77
12. INVESTIGATOR AGREEMENT .....	79
13. REFERENCES .....	80
14. APPENDICES .....	85
14.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status .....	85
14.2 List of Strong and Moderate CYP3A Inhibitors .....	85
14.3 Cockcroft-Gault Equation .....	86
14.4 Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1) .....	86
14.5 Amendment 1 Detailed Summary of Changes .....	87

**LIST OF TABLES**

Table 6-1	Alisertib Combined With Paclitaxel for Phase 1 Dose Escalation .....	42
Table 6-2	Dose Modification Rules: Hematological Toxicity .....	46
Table 6-3	Dose Adjustments for Oral Mucositis (Drug-related) .....	47

**LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS**

<b>Abbreviation</b>	<b>Term</b>
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration versus time curve
AUC <sub>0-inf</sub>	area under the plasma concentration versus time curve from zero to infinity
AUC <sub>0-tlast</sub>	area under the plasma concentration versus time curve zero to the time of the last measurement
AUC <sub>0-τ</sub>	area under the plasma concentration versus time curve from zero to next dose
β-hCG	beta-human chorionic gonadotropin
BID	<i>bis in die</i> ; twice daily
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CL	clearance, IV dosing
CL/F	apparent oral clearance
C <sub>max</sub>	single-dose maximum (peak) concentration
CNS	central nervous system
CO <sub>2</sub>	carbon dioxide
CR	complete response
CRM	continual reassessment method
CT	computed tomography
CYP	cytochrome P450
DL	dose level
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ECT	enteric-coated tablet

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

<b>Abbreviation</b>	<b>Term</b>
EDC	electronic data capture
EOS	End of Study (visit)
EOT	End of Treatment (visit)
ES-SCLC	extensive-stage small cell lung cancer
EU	European Union
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practices
Hct	hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
K <sub>i</sub>	inhibition constant
LDH	lactate dehydrogenase
LS-SCLC	limited-stage small cell lung cancer
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OC	ovarian cancer
OS	overall survival

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

Abbreviation	Term
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)
PO	<i>per os</i> ; by mouth (orally)
PR	partial response
QD	<i>quaque die</i> ; once daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCLC	Small cell lung cancer
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
$T_{max}$	first time of occurrence of maximum (peak) concentration
TSH	Thyroid stimulating hormone
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
WBC	white blood cell
WHO	World Health Organization

## **1. BACKGROUND AND STUDY RATIONALE**

### **1.1 Scientific Background**

#### **1.1.1 Study Drug**

Alisertib (International Nonproprietary Name; also known as MLN8237) is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of Aurora A kinase. A selective small molecule inhibitor of Aurora A kinase, alisertib is being developed for the treatment of advanced malignancies, as Aurora A is expressed in all actively dividing cells. Aurora A is localized to centrosomes and the proximal mitotic spindle during mitosis, where it functions in a diverse set of mitotic processes. It is expected to have potential application across a broad range of human tumors, given the central role of mitosis in the progression of virtually all malignancies. Indeed, alisertib has demonstrated activity against a broad range of both in vitro and in vivo nonclinical tumor models, as described briefly in Section 1.2.

### **1.2 Nonclinical Experience**

#### **1.2.1 In Vitro Pharmacology**

Alisertib is an ATP-competitive and reversible inhibitor of Aurora A kinase in vitro with an inhibition constant ( $K_i$ ) of 0.43 nM.<sup>(2)</sup> The data from both enzymatic and cell-based assays demonstrated that alisertib is a selective and potent inhibitor of Aurora A kinase.<sup>(2, 3, 4, 5, 6)</sup> Alisertib (administered as the salt form MLN8237-004 or as the free acid MLN8237-001) inhibited proliferation of a wide variety of tumor cell lines grown in culture.<sup>(7)</sup> Moreover, treatment of tumor cell lines with alisertib induced phenotypes consistent with Aurora A kinase inhibition, including mitotic spindle defects, mitotic delay, and apoptosis.<sup>(3, 7, 8, 9, 10, 11, 12, 13)</sup> For further details, refer to the Investigator's Brochure (IB).

#### **1.2.2 In Vivo Pharmacology**

Alisertib demonstrated antitumor activity when administered orally on a daily basis for approximately 21 days (maximal tumor growth inhibition [TGI] > 90%) in several experimental solid and hematologic human tumor models grown as xenografts in immunocompromised mice.<sup>(14, 15, 16, 17, 18, 19, 20)</sup> The maximally efficacious dose for each model varied: between 10 and 30 mg/kg if given once daily (QD) and 20 mg/kg if given twice daily (BID). Studies in the HCT-116 colon tumor model showed that less frequent dosing (eg, 5 days on followed by 5 days off) was also efficacious, demonstrating that continuous dosing is not necessary for antitumor activity.<sup>(15)</sup> A single oral dose of alisertib

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

given to nude mice bearing subcutaneous HCT-116 human colon tumors resulted in inhibition of activated Aurora A kinase and an increase in mitotic cells.<sup>(21)</sup> The relationship between pharmacokinetics (PK), pharmacodynamics, and efficacy was further studied in HCT-116 xenografts using oral dosing and subcutaneous osmotic minipumps.<sup>(21)</sup> Both a pharmacodynamic response and efficacy (antitumor activity) were achieved using either route of administration. The data from these studies suggest that the maximum pharmacodynamic effect (mitotic accumulation) and efficacy are achieved at 1- $\mu$ M steady-state plasma concentrations. Moreover, the maximally efficacious oral dose of alisertib in the HCT-116 model (30 mg/kg QD) resulted in plasma concentrations of 1  $\mu$ M for 8 to 12 hours postdose. Plasma concentrations of alisertib associated with saturating levels of pharmacodynamic and antitumor activity (1  $\mu$ M) were exceeded at the recommended phase 2 dose of alisertib in patients (50 mg BID). For further details, refer to the IB.

### **1.2.3 Safety Pharmacology and Toxicology**

Safety pharmacology studies with alisertib did not identify significant adverse effects in nonclinical studies, including in the central nervous system (CNS) and cardiovascular systems.<sup>(22, 23)</sup> No alisertib-related effects on clinical signs or physical examination findings indicative of impaired respiratory function (ie, labored or shallow breathing), or microscopic changes in the lungs of animals that survived until scheduled termination, were noted at tolerated doses in Good Laboratory Practice (GLP)-compliant, repeat-dose, toxicology studies.<sup>(24, 25, 26, 27)</sup> Alisertib exhibited minimal activity against the human *ether-à-go-go*-related gene current (concentration producing 50% inhibition and  $K_i > 100 \mu$ M).<sup>(28)</sup> Alisertib (administered as the free acid, MLN8237-001) had in vitro activity against the gamma aminobutyric acid alpha 1 benzodiazepine binding site ( $K_i = 290 \text{ nM}$ ).<sup>(29)</sup>

The dose-limiting toxicities (DLTs) for alisertib in both rats and dogs after repeat daily oral dosing for 2 cycles (each cycle consisted of 7 consecutive days separated by a 14-day dose holiday) or for 6 cycles (each cycle consisted of 21 consecutive days of dosing separated by a 7-day dose holiday) were consistent with inhibition of Aurora A kinase by alisertib.<sup>(24, 25, 26, 27)</sup> Principal findings in toxicology studies in rats and dogs included gastrointestinal (GI) signs, panleukopenia, decreased reticulocyte counts, and increased mitotic figures, and apoptosis (single-cell necrosis) in tissues with a high basal cellular replication rate. These findings are indicative of toxicity to rapidly replicating cell populations and are consistent with the outcomes associated with Aurora A kinase inhibition.<sup>(30)</sup> No off-target effects were seen in the GLP-compliant toxicology studies.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

When tested for genotoxicity, alisertib was negative for mutagenicity using the bacterial reverse mutation assay (Ames assay) both in the absence and presence of Aroclor™ 1254-induced rat liver S9 fractions.<sup>(31)</sup>

In a rat bone marrow micronucleus assay, alisertib was considered to be equivocal for clastogenicity.<sup>(32)</sup> For further details, refer to the IB.

### **1.3 Clinical Experience**

Clinical experience to date includes 20 company-sponsored clinical studies of alisertib that are in progress or have been completed, as follows: 11 single-agent phase 1 studies (Studies C14001, C14002, C14003, C14010, C14013, C14014, C14015, C14017, C14019, TB-MA010030, and TB-MA010033); 3 single-agent phase 2 studies (Studies C14004, C14005, and C14006); 1 single-agent phase 1/2 study (Study C14007); 1 single-agent phase 3 study (Study C14012); and 4 combination studies (Studies C14008 [phase 1/2] with paclitaxel, C14009 [phase 1] with docetaxel, C14011 [phase 1/2] with either rituximab or rituximab + vincristine, and C14018 [phase 2] with paclitaxel).

As of 29 March 2014, a total of 1103 patients have received alisertib in company-sponsored studies. The clinical safety data include experience from patients who received multiple cycles followed by treatment-free periods between each cycle, and experience from patients who reduced or discontinued treatment. Drug abuse, dependency, and drug withdrawal effects were not observed in the available clinical data.

Adverse events (AEs) observed as of 29 March 2014 are generally reversible, dose dependent, and consistent with the pharmacologic profile of alisertib as an antimitotic agent with predominant effects in proliferative tissues. Adverse events were generally manageable with standard medical intervention and dose reduction as needed. The more commonly observed ( $\geq 30\%$  incidence) treatment-emergent AEs (TEAEs) from pooled data across the alisertib single-agent studies include neutropenia (47%), fatigue (46%), anemia (45%), diarrhea (42%), alopecia (35%), nausea (32%), and stomatitis (31%). The more commonly observed ( $\geq 30\%$  incidence) treatment-emergent AEs (TEAEs) from Study C14008 of alisertib plus paclitaxel include neutropenia (71%), diarrhea (69%), fatigue (63%), stomatitis (57%), anemia (52%), nausea (51%), alopecia (47%), constipation (34%), vomiting (32%), leucopenia (31%), and abdominal pain (30%). When compared to patients treated with alisertib alone, patients treated with alisertib plus paclitaxel experienced a greater frequency of  $\geq$  Grade 3 treatment-related neutropenia, stomatitis, and

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

diarrhea. For alisertib plus paclitaxel the frequency was: neutropenia (62%), stomatitis (19%), and diarrhea (7%), and for alisertib alone the frequency was: neutropenia (38%), stomatitis (9%), and diarrhea (3%). No unanticipated toxicities were reported, and no increased rate of peripheral neuropathy when alisertib was added to paclitaxel.

The predominant toxicities reflect the mechanism of action in proliferating tissues (bone marrow, gastrointestinal epithelium, and hair follicles). The suggested management of these toxicities is based on standard clinical paradigms for an antiproliferative chemotherapeutic agent. Using a treatment-free period for recovery between each cycle of drug administration, the clinical experience from multiple phase 1 through 2 studies indicates that major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 12 to 24 months. Except for alopecia, the predominant toxicities are largely reversible, can be monitored by routine clinical examinations, and are manageable by dose reduction or supportive care.

Central nervous system effects, including transient dose-dependent somnolence and confusion, have also been observed. These CNS effects may not be associated with Aurora A kinase inhibition but instead likely represent benzodiazepine-like effects of alisertib due to its structural similarity to benzodiazepine. At higher dose levels evaluated in phase 1 studies, severe CNS effects were sometimes considered DLTs, although these effects abated during the planned treatment-free period. In the phase 1 studies, CNS effects appeared to be related to high peak plasma levels resulting from single daily doses of alisertib. The frequency and/or severity of benzodiazepine-associated CNS toxicities may be reduced in adult patients enrolled in recent studies that administered alisertib with divided doses (eg, BID), a schedule designed to reduce peak plasma levels while maintaining overall area under the plasma concentration versus time curve (AUC). Overall, CNS effects were generally reversible and manageable by dose delay or reduction, and some patients have been managed by dose reduction of other sedative medications.

Following oral administration of alisertib as the enteric-coated tablet (ECT) formulation, peak concentrations of alisertib were generally achieved by 3 hours postdose. The terminal half-life ( $t_{1/2}$ ) was approximately 21 hours following 7 days of multiple dosing. Steady-state plasma exposures of alisertib increased in an approximately dose-proportional manner over the range of 5 to 200 mg/day in patients with advanced solid tumors. Alisertib is metabolized by multiple cytochrome P450 (CYP) isozymes (CYP3A4, 2C8, 2C9, 2C19, and 1A2) and uridine diphosphate-glucuronosyltransferase (UGT) isozymes (UGT1A1, 1A3, and 1A8). Based on preliminary results of a population PK analysis in 363 adult cancer

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

patients, the apparent oral clearance (CL/F) of alisertib was unaffected by age, body weight, body surface area (BSA), or UGT1A1 genotype (number of \*28 alleles).

In Study C14008 the effect of alisertib on paclitaxel PK was assessed at the Western recommended phase 2 dose (RP2D) of 40 mg BID of alisertib plus 60 mg/m<sup>2</sup> of paclitaxel. Based on the preliminary data, it appears that there is a small (10%-19%) increase in paclitaxel total systemic exposures (AUC) achieved when co-administered with 40 mg BID alisertib. The exposures of paclitaxel achieved at 60 mg/m<sup>2</sup> when co-administered with 40-mg BID alisertib are not higher than those achieved with paclitaxel when administered alone at the standard single-agent weekly dose of 80 mg/m<sup>2</sup>, indicating the lack of any clinically concerning increases in paclitaxel exposures when co-administered with alisertib at the RP2D of the combination.

Pharmacokinetic data are available from 3 completed single-agent, phase 1 studies designed to evaluate the safety, tolerability, and PK of alisertib in Asian patients (22 Japanese patients [TB MA010030 and TB-MA010033], and 34 East Asian patients [C14013]). Across a total of 56 patients from these 3 phase 1 studies in Asian patients, the geometric mean dose-normalized steady-state AUC was 67% higher than the corresponding geometric mean dose-normalized steady-state AUC in the Western population (N = 363). Consistent with these PK results, the maximum tolerated dose (MTD) of single-agent alisertib in East Asian patients was determined to be 30 mg BID and is 40% lower than the Western MTD of 50 mg BID.

Further details on alisertib clinical experience are provided in the IB.

**1.4 Disease Under Treatment****1.4.1 Epithelial Ovarian Cancer Epidemiology and Treatment**

Ovarian cancer (OC) continues to be the leading cause of death from gynecological malignancies and ranks as the fourth most common cause of cancer mortality in women. In 2010, more than 9900 new cases of OC were reported in Japan, with over 4600 deaths estimated by Center for Cancer Control and Information Services, National Cancer Center, Japan.<sup>(33)</sup> Unfortunately, in most patients, OC is diagnosed at advanced stages, indicating spread beyond the pelvis at the time of diagnosis. Disease dissemination results in significant morbidity and impaired survival in comparison with those who have disease diagnosed while it is still confined to the ovaries (Stage I), in whom over 90% survival can

## **Alisertib (MLN8237)**

### **Clinical Study Protocol C14022 Amendment 01**

be achieved largely with surgical intervention. Patients with advanced-stage disease have 5-year overall survival (OS) rates ranging from 20% to 30%.

Systemic treatments commonly employ a combination of platinum and taxane chemotherapy. Strategies incorporating biological and targeted agents continue to evolve. Unfortunately, most (up to 70%) patients who present with advanced-stage disease exhibit recurrent or persistent disease following primary treatment.

#### **1.4.2 Small Cell Lung Cancer**

The annual estimation of lung cancer incidence in Japan is about 107,000.<sup>(33)</sup> Small cell lung cancer (SCLC) accounts for approximately 13% to 15% of all lung cancers diagnosed, representing around 15,000 in Japan.<sup>(34, 35, 36)</sup> This is a devastating disease where patients are rarely cured and the long-term survival rate (beyond 5 years) is dismal at less than 5%.<sup>(37)</sup>

SCLC is an aggressive malignant disease. At the time of diagnosis, 70% of patients will have extensive-stage (ES)-SCLC, and for these patients the prognosis is poor, with a median survival of 8 to 10 months and less than 10% surviving 2 years after standard first-line treatment.<sup>(34)</sup>

Platinum-based combinations are the accepted first-line therapy for SCLC. Despite being initially chemosensitive with response rates of around 60% to 80%, relapse is almost universal; of the limited-stage (LS)-SCLC patients, approximately 85% will relapse, and for the ES-SCLC patients, almost all patients will relapse. Topotecan is the accepted standard treatment for relapsed patients worldwide and is the only drug that has regulatory approval in the EU and the US for second-line therapy. Paclitaxel has also shown activity in the resistant relapse population and its use as an active agent for this disease is supported by the NCCN and ESMO guidelines.<sup>(38, 39, 40, 41)</sup>

#### **1.5 Study Rationale**

In experimental system, modulation of Aurora kinase activity in ovarian or other cancer models has been studied, including work with taxane combination treatments with tumor cells in vitro and in vivo xenografts.<sup>(42)</sup> These experiments generally demonstrated tumor cell apoptosis and delay or regression in xenograft models. Blockade of Aurora kinase signaling enhanced the antitumor activity of chemotherapy, including taxanes in OC models.<sup>(43, 44, 45)</sup> Targeting the mitotic apparatus by 2 complementary mechanisms of action

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

by combining alisertib with a known active agent such as paclitaxel is a rational approach to treating patients.

The phase 1 dose ranging portion of Study C14008, a phase 1/2 study of the combination of alisertib and paclitaxel in patients with advanced ovarian and breast cancer, has been completed. The combination was found to be tolerable, with manageable toxicity and without occurrence of unknown or unexpected toxicities. A RP2D of alisertib 40 mg BID (3 days on/4 days off for 3 weeks) on Days 1 through 3, 8 through 10, 15 through 17 plus paclitaxel 60 mg/m<sup>2</sup> on Days 1, 8, and 15 in a 28-day cycle was determined. Preliminary results in 49 patients enrolled in the phase 1 portion showed objective responses in 17 (44%) patients (11 with OC and 6 with breast cancers), including 1 complete response (CR) and 16 partial responses (PR). This combination is being investigated in 2 randomized phase 2 studies including the phase 2 portion of Study C14008 in relapsed/refractory OC patients and Study C14018 in relapsed/refractory SCLC patients.

The present study is an open-label, phase 1b, dose-finding study of alisertib combined with 60 mg/m<sup>2</sup> weekly paclitaxel to be conducted in East Asian patients (ie, patients from countries including but not limited to Japan, Taiwan, and South Korea) with advanced solid tumors. The MTD/RP2D of alisertib combined with weekly paclitaxel was determined in Western patients in Study C14008. As discussed in the following section, single-agent phase 1 studies of alisertib in East Asian/Japanese patient populations have indicated that systemic exposures of alisertib are approximately 70% higher than in Western patient populations, translating to a 40% lower single-agent MTD in East Asian patients compared to Western patients. The MTD of alisertib in combination with 60 mg/m<sup>2</sup> weekly paclitaxel in East Asian patients has not yet been determined. Based on the observed PK and dose differences between East Asian/Japanese and Western populations for single-agent alisertib, it can be expected that the MTD of alisertib in combination with paclitaxel would be lower than that determined for this combination in Western patients in Study C14008. Accordingly, this study is intended to characterize the PK, safety, and tolerability and to determine the MTD/RP2D of alisertib in combination with 60 mg/m<sup>2</sup> weekly paclitaxel in East Asian patients to support global clinical development.

## **1.6 Dose Rationale**

In Study C14008, the RP2D of alisertib combined with weekly paclitaxel in Western patients was alisertib 40 mg BID on Days 1-3, 8-10, and 15-17 plus paclitaxel 60 mg/m<sup>2</sup> on Days 1, 8, and 15 in a 28-day cycle. While no new or unanticipated toxicities were reported

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

in the combination arm, there was an increased incidence for some AEs, including neutropenia, diarrhea, and stomatitis with a higher incidence of Grade 3 or higher treatment related AEs of neutropenia and stomatitis.

Preliminary alisertib PK data in Japanese/East Asian patients across 3 phase 1 studies (TB-MA010030 and TB-MA010033 in Japanese patients; C14013 in East Asian patients of Chinese and Korean races) have indicated approximately 70% higher dose-normalized systemic exposure to single-agent alisertib when compared with exposures in Western patients. Therefore, an alisertib dose of 20 or 25 mg BID in East Asian patients is expected to achieve exposures comparable to the range of exposures achieved in the Western population at the MTD/RP2D of the combination (ie, 40 mg BID alisertib plus 60 mg/m<sup>2</sup> paclitaxel). Escalation beyond 25 mg BID is not expected to be necessary in the dose escalation part of this combination study as higher alisertib doses in the East Asian patient population would be expected to result in systemic exposures higher than those observed at the Western MTD/RP2D of 40 mg BID. However, if alisertib exposures in the combination setting in the East Asian population are unexpectedly lower than anticipated from single-agent experience in East Asian patients, and no DLTs have occurred in the dose level (DL) 2 cohort (alisertib 25 mg BID plus 60 mg/m<sup>2</sup> paclitaxel), the alisertib dose may be escalated further following discussion between the investigator and the sponsor pending PK and safety assessment.

The dose of paclitaxel will remain constant throughout the study and will be administered IV at a dose of 60 mg/m<sup>2</sup> on Days 1, 8, and 15 in 28-day cycles. In Study C14008, escalation beyond 10 mg BID alisertib was limited by overlapping antiproliferative mechanistic toxicities (eg, myelosuppression) when alisertib was added to 80 mg/m<sup>2</sup> weekly paclitaxel. Based on preliminary PK results, exposures of alisertib achieved at 10 mg BID in combination with 80 mg/m<sup>2</sup> weekly paclitaxel (administered on Days 1, 8, and 15 in 28-day cycles) were below the pharmacodynamically active range of exposures based on prior understanding of the exposure-tumor pharmacodynamics relationship for single-agent alisertib. Based on these considerations, a dose of 60 mg/m<sup>2</sup> weekly paclitaxel will be used in this study.

## **1.7 Potential Risks and Benefits**

In company-sponsored studies as of 29 March 2014, 1103 patients have been treated with alisertib. The clinical safety data include experience from patients who received multiple cycles followed by treatment-free periods between each cycle, and experience from patients

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

who reduced or discontinued treatment. Drug abuse, dependency, and drug withdrawal effects were not observed in the available clinical data.

To date, the observed risks associated with alisertib treatment, as detailed in Section 6 and the Safety Management Attachment to the IB, include (1) reversible myelosuppression, including leukopenia, neutropenia, febrile neutropenia, lymphopenia, thrombocytopenia, and anemia; (2) GI toxicity, including stomatitis/mucositis/oral pain, nausea, vomiting, anorexia, abdominal pain, dyspepsia, diarrhea, and dehydration; (3) sedation, somnolence, confusional state, disorientation (and associated memory loss), and gait disturbances; (4) alopecia; (5) asthenia/fatigue; (6) fever; (7) infection; (8) abnormal liver function tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT); and (9) skin disorders (eg, rash, which may include bullous dermatitis) and palmar-plantar erythrodysesthesia syndrome. One case of hepatic veno-occlusive disease has also been observed.

To mitigate the inherent risks in clinical studies of alisertib, patients are evaluated frequently while they are receiving treatment.

For details regarding management of specific clinical events, refer to Section 6.5.

## **2. STUDY OBJECTIVES**

### **2.1 Primary Objectives**

The primary objectives are:

- To evaluate the safety and tolerability and determine the MTD to subsequently define an RP2D of alisertib in combination with weekly paclitaxel in East Asian patients with advanced solid tumors
- To characterize the PK of alisertib and paclitaxel in the combination setting in East Asian patients with advanced solid tumors

## **2.2 Secondary Objective (For Expansion Only)**

The secondary objective is:

- To identify initial signs of antitumor activity in patients with relapsed/refractory OC or SCLC

## **3. STUDY ENDPOINTS**

### **3.1 Primary Endpoints**

The primary endpoints are:

- AEs, serious adverse events (SAEs), assessment of clinical laboratory values and vital sign measurements – dose escalation and dose expansion
- PK parameters of alisertib, including but not limited to, maximum plasma concentration ( $C_{max}$ ), first time of occurrence of maximum (peak) concentration ( $T_{max}$ ) and area under the plasma concentration versus time curve zero to the next dose ( $AUC_{0-\tau}$ ); PK parameters of paclitaxel, including but not limited to,  $C_{max}$ , area under the plasma concentration versus time curve zero to the time of the last measurement ( $AUC_{0-t_{last}}$ ), area under the plasma concentration versus time curve from zero to infinity( $AUC_{0-\infty}$ ) (if data permit), and  $t_{1/2}$  (if data permit), when administered alone and during concomitant administration of alisertib – dose escalation and dose expansion

### **3.2 Secondary Endpoint**

The secondary endpoint is:

- Disease response based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 overall response rate (ORR) (CR + PR) - dose expansion only

## **4. STUDY DESIGN**

### **4.1 Overview of Study Design**

This is an open-label, multicenter, phase 1b study to evaluate the safety, tolerability, and PK of alisertib in combination with weekly paclitaxel in East Asian patients. The study is in 2 parts: the first part is a dose escalation to determine the MTD and define the RP2D of the alisertib plus paclitaxel combination in East Asian patients with advanced solid tumors; the second part is an expansion cohort at the RP2D of the alisertib plus paclitaxel combination in East Asian patients with either OC or SCLC.

It is expected that approximately 30 patients will be enrolled into this study. Alisertib will be administered orally 3 days on/4 days off for 3 weeks on Days 1 through 3, 8 through 10, and 15 through 17 in 28-day cycles. Paclitaxel 60 mg/m<sup>2</sup> IV will be administered on Days 1, 8, and 15 in 28-day cycles. The paclitaxel dose will remain constant throughout the dose escalation and expansion parts of this study.

Enrolled patients may receive study drug until observed progression, need of discontinuation because of toxicity, lost to follow-up, study is terminated by the sponsor, protocol violation, unsatisfactory therapeutic response, or voluntary withdrawal by the patient from the study. Patients may discontinue therapy at any time. Patients will attend the End of Treatment visit 30 days after receiving their last dose of study drug.

A dose escalation (3 + 3 schema) will be used to determine the MTD and the RP2D of the combination (as detailed in Section 6.4), which will be further evaluated in the expansion part of the study. The starting dose will be 15 mg BID alisertib (DL1); the next planned dose level is 25 mg BID alisertib (DL2). If  $\geq 2$  patients experience a DLT at 25 mg, alisertib will be de-escalated, and an intermediate dose level of alisertib 20 mg BID (DL3-intermediate) will be explored. The MTD/RP2D will require first-cycle DLTs in not more than 1 in 6 DLT-evaluable patients enrolled in a given dose level. If  $\geq 2$  of the first 6 patients experience a DLT at DL1, depending on the overall safety profile, the type of AEs/DLTs observed, and the available PK data, a decision will be made either to expand the 15 mg BID alisertib (DL1) cohort with 6 additional patients, or to de-escalate the alisertib dose to 10 mg BID (DL-1), or to terminate the study. In the case of an expansion of the DL1 cohort, a tolerable dose will then require first-cycle DLTs in no more than 3 of 12 DLT-evaluable patients to confirm the MTD. If alisertib exposures in the combination setting in the East Asian population are unexpectedly lower than anticipated from single-agent experience in East Asian patients, and no DLTs have occurred in the DL2 cohort

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

(alisertib 25 mg BID plus 60 mg/m<sup>2</sup> paclitaxel), the alisertib dose may be escalated further following discussion between the investigator and the sponsor pending PK and safety assessment. Should more data be needed to better understand the observed safety and/or PK, with the agreement of the sponsor's project clinician (or designee), cohort(s) at any dose level may be expanded. Intrapatient dose escalation will not be permitted in this study. It is planned that at least 1 Japanese patient will be included in each of the dose levels explored.

The effect of concomitant administration of alisertib on paclitaxel PK will be evaluated in this study. To this effect, alisertib doses will be held on Days 1 through 3 in Cycle 2 so that paclitaxel PK can be evaluated, in the absence of alisertib, following paclitaxel dose administration on Cycle 2, Day 1. Paclitaxel PK data on Cycle 2, Day 1 will serve as a reference for comparison with paclitaxel PK, evaluated at Cycle 1, Day 1 in the presence of alisertib. During the dose escalation and expansion part, for Cycle 2 only, patients will receive 12 doses of alisertib, administered BID on Days 8 through 10 and 15 through 17. The effect of alisertib on paclitaxel PK will be assessed in a minimum of 12 patients who complete protocol-specified dosing and PK measurements in the first 2 treatment cycles at the RP2D of the combination (dose escalation and expansion part). Blood draws will be taken as detailed in the [Schedule of Events](#) and Section [7.4.17](#).

Pharmacokinetics of alisertib will be evaluated on Days 1 and 3 in Cycle 1 for both the dose escalation and expansion parts of the study. Blood draws will be taken as detailed in the [Schedule of Events](#) and Section [7.4.17](#).

An MTD should be established and then a RP2D will be defined based on all relevant considerations/parameters (eg, safety, tolerability, and PK).

After dose escalation has completed, a minimum of 12 patients with relapsed/refractory OC or SCLC will be enrolled into the dose expansion part of the study. During dose expansion, safety, tolerability, and initial signs of activity at the RP2D will be evaluated.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010.<sup>(1)</sup> Dose-limiting toxicities (DLTs) are defined in Section [6.3](#).

Adverse events will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of alisertib in combination with paclitaxel.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

Patients cannot have received antineoplastic therapy or radiotherapy within the 3 weeks before enrollment (14 days for regimens with recovery expected within 7-14 days).

For all patients, scans (ie, CT and/or MRI) will be read locally. The investigator-assessed CR + PR (based on RECIST 1.1 criteria) will be used for efficacy assessment.

**4.2 Number of Patients**

Approximately 30 patients will be enrolled in this study, including a minimum of 12 patients with epithelial OC and SCLC (combined) in the expansion cohort.

There will be approximately 2 to 3 study centers in the escalation part and approximately 10 study centers in the expansion part. All study centers will be in East/North Asia and will include 2 sites in Japan. A patient is considered enrolled in the study when the patient receives the first dose of alisertib.

For MTD assessment, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced.

**4.3 Duration of Study**

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

Patients will be followed for 30 days after the last dose of alisertib plus paclitaxel or the start of subsequent anticancer therapy to permit the detection of any delayed treatment-related AEs. The pharmacokinetic analyses will be conducted after all patients enrolled in the study have had the opportunity to complete 2 cycles of treatment with alisertib plus weekly paclitaxel. The final analysis for the clinical study report will be conducted after all patients enrolled in the study have had the opportunity to complete 1 year of treatment with alisertib plus weekly paclitaxel or discontinue the study treatment.

It is anticipated that this study will last for approximately 24 months. The study will be closed once all the enrolled patients in the expansion part complete or discontinue from the study.

## **5. STUDY POPULATION**

### **5.1 Inclusion Criteria**

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

1. Male or female patients 18 years or older (or minimum age of legal consent consistent with local regulations) at the time written study informed consent is obtained.
2. Patients of East Asian ethnicity (eg, Chinese, Japanese, or Korean).
3. Patients must have a diagnosis of a solid tumor malignancy (escalation part) or relapsed or refractory OC or SCLC (expansion part).
  - Patients in the expansion cohort must have a pathologically (histology or cytology) confirmed diagnosis of either OC (including recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer) or SCLC, which is measurable disease as per RECIST, version 1.1.
  - Patients in the expansion cohort must not have received more than 2 prior taxane-containing regimens.
4. No antineoplastic therapy (eg, drugs, biologicals, monoclonal antibodies, etc) or radiotherapy within the 3 weeks before enrollment (14 days for regimens with recovery expected within 7 to 14 days). The patient must have recovered (ie,  $\leq$  Grade 1 toxicity or patient's baseline status, except alopecia) from all treatment-related toxicities.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Section 14.1).
6. Adequate bone marrow function as defined by:
  - Absolute neutrophil count (ANC)  $\geq$  1,500 cells/mm<sup>3</sup> (without need for growth factor support).
  - Platelet count  $\geq$  100,000 cells/mm<sup>3</sup> (without need for transfusion or growth factor support).

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

- Hemoglobin level  $\geq$  9 g/dL.

7. Adequate liver function as defined by:

- Bilirubin  $<$  1.5 times the upper limit of normal (ULN)
- ALT and AST  $\leq 2.5 \times$  ULN ( $\leq 5 \times$  ULN if due to liver metastases)
- Serum albumin equal to or greater than the lower limit of normal

8. Adequate renal function as defined by:

- Creatinine  $< 1.5 \times$  institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula  $\geq 30$  mL/minute for patients with creatinine levels above institutional ULN (can be calculated using serum creatinine value; see Section 14.3).

9. Patients must have received at least 1 prior chemotherapy regimen, but no more than 2 previous chemotherapy regimens for the advanced and/or metastatic stage disease. The neo-adjuvant chemotherapy or post-surgical adjuvant chemotherapy for early-stage disease would not be counted.

10. Female patients who:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug
- Adhere to any treatment-specific pregnancy prevention guidelines for paclitaxel

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
- Adhere to any treatment-specific pregnancy prevention guidelines for paclitaxel.

11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. Suitable venous access for the study-required blood sampling, including PK.
13. Ability to swallow tablets.

## **5.2 Exclusion Criteria**

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

1. Patients with carcinomatous meningitis.
2. Patients with symptomatic and/or progressive brain metastases or treatment with brain edema.
3. Known hypersensitivity to Cremophor® EL, paclitaxel, alisertib or their components.
4. Prior treatment with an Aurora A specific-targeted or pan-Aurora-targeted agent, including alisertib in any setting.
5. Prior history of  $\geq$  Grade 2 neurotoxicity or any toxicity requiring discontinuation from taxane chemotherapy that is not resolved to  $\leq$  Grade 1.
6. Patients who received prior weekly taxane-based therapy with early disease progression during or within 1 month of completing therapy (refractory disease).
7. Any comorbid condition or unresolved toxicity that would preclude administration of weekly paclitaxel.
8. Systemic treatment with moderate or strong CYP3A inhibitors must be discontinued at least 14 days before the first dose of alisertib, and the use of these agents is not permitted during the study.
9. Known GI abnormality (including recurrent nausea or vomiting) or GI procedure that could interfere with or modify the oral intake, absorption, or tolerance of alisertib.
10. Patients requiring treatment with clinically significant enzyme inducers, such as the enzyme-inducing antiepileptic drugs phenytoin, carbamazepine, phenobarbital, oxcarbazepine, primidone, rifampin, rifabutin, rifapentine, or St. John's wort within

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

14 days before the first dose of alisertib or requiring the use of these medications during the study.

11. Requirement for administration of proton pump inhibitor (PPI), H2 antagonist (premedication for paclitaxel allowed), or pancreatic enzymes. Use of any PPI in either continued or intermittent use will be prohibited during the conduct of the study and patients must not use a PPI within 5 days of the first dose of alisertib.
12. Life-threatening or severe CNS, pulmonary, renal, or hepatic disease unrelated to cancer, or any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
13. Treatment with any investigational products within 5 half-lives before the first dose of study drug.
14. Treatment with fully human or chimeric monoclonal antibodies within 42 days before the first dose of study drug (21 days if clear evidence of progression).
15. Major surgery within 14 days before the first dose of study drug.
16. Infection requiring systemic intravenous (IV) antibiotic therapy within 14 days preceding the first dose of study drug, or other severe infection.
17. Known human immunodeficiency virus (HIV) positive.
18. Known hepatitis B surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have positive hepatitis B core antibody can be enrolled but must have an undetectable hepatitis B viral load. Patients who have positive hepatitis C antibody must have an undetectable hepatitis C viral load.
19. History of myocardial infarction, unstable symptomatic ischemic heart disease, uncontrolled hypertension despite appropriate medical therapy, or cardiac arrhythmias, thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy) within 6 months before receiving the first dose of study drug. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed. Patients with a pacemaker may be enrolled in the study upon discussion with the project clinician.

20. Female patients who are in the lactation period or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day1 before the first dose of study drug.
21. Diagnosed with or treated for another malignancy within 3 years before the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type may be enrolled in the study if they have undergone complete resection and no evidence of active disease is present.

## **6. STUDY DRUG**

### **6.1 Study Drug Administration**

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

Alisertib will be administered orally 3 days on/4 days off for 3 weeks on Days 1 through 3, 8 through 10, and 15 through 17 in 28-day cycles. Alisertib dosing during Cycle 1 will begin at Cycle 1, Day 1, the same day as the first dose of paclitaxel; alisertib will be administered 1 hour before the start of the paclitaxel infusion. In Cycle 2, alisertib doses will be held on Days 1 through 3. During the dose escalation and expansion part, for Cycle 2 only, patients will receive 12 doses of alisertib, administered BID on Days 8 through 10 and 15 through 17 to permit PK assessment of paclitaxel alone up to 48 hours ([Alisertib and Paclitaxel PK Sampling Schedule](#)). Alisertib dosing in all subsequent cycles (Cycle 3 and beyond) will begin on Day 1.

Patients will be instructed to take each PO dose of alisertib with 8 ounces (1 cup, 240 mL) of water. The 2 daily doses must be taken at least 6 hours apart. Alisertib should be administered on an empty stomach in the first 3 days of Cycle 1 (no food from 2 hours before the dose until 1 hour after the dose). Patients should be instructed to take their alisertib study medication at approximately the same time each day, approximately 12 hours apart (eg, 08:00 and 20:00) but not less than 6 hours apart, and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it before swallowing.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

Alisertib will be supplied as 10- and 15-mg ECTs with the dose strength expressed as milligrams of active drug (free acid); other strengths may be supplied depending on the observed MTD. All tablets are to be ingested whole; patients who have difficulty swallowing tablets will be excluded from the study. Anti-emetic agents may be administered at the discretion of the investigator. Although not prohibited, the use of benzodiazepines for the prophylaxis or treatment of nausea or vomiting is discouraged because of the potential benzodiazepine-like effects of alisertib.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

**6.2 Reference/Control Therapy****6.2.1 Paclitaxel**

Paclitaxel will be administered as an IV infusion over at least 1 hour (but not more than 90 minutes) with a dose of 60 mg/m<sup>2</sup> on Days 1, 8, and 15 in 28-day cycles. On Cycle 1, Day 1 and Cycle 2, Day 1, the paclitaxel dose should be administered over 60 minutes (it must not be less than 60 minutes, but may be up to 70 minutes maximum, where necessary). The paclitaxel dose will remain constant throughout the study. The paclitaxel infusion time is 1 hour; the infusion time may be modified if required after review and agreement by the project clinician. Refer to the paclitaxel product label for further details regarding paclitaxel administration.

**6.2.2 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. Premedications that may be used in this setting can include: corticosteroid (eg, dexamethasone, as a 20-mg single dose, which can be reduced with subsequent paclitaxel cycles); diphenhydramine; a 5-hydroxytryptamine 3 (5-HT<sub>3</sub>) serotonin receptor antagonist antiemetic administered at its labeled dose. Benzodiazepines are to be avoided. Brief administration of histamine-2 antagonists (such as a single dose of cimetidine or ranitidine) is allowed if required on the day of paclitaxel administration, but prolonged administration of a histamine-2 antagonist (or any other agent that can alter stomach pH or drug absorption) is to be avoided (see Section 6.6). Modifications to paclitaxel administration are allowed upon agreement by the project clinician and will be documented in the electronic case report form (eCRF).

### **6.3 Definitions of Dose-Limiting Toxicity**

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010.<sup>(1)</sup> These criteria are provided in the Study Manual. Dose-limiting toxicity will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with alisertib plus paclitaxel. See also Section 6.5.3 for toxicities considered to be DLTs if they occur during the dosing period in the first cycle.

1. Grade 4 neutropenia (ANC < 500 cells/mm<sup>3</sup>) lasting more than 7 consecutive days.
2. Grade 4 neutropenia associated with coincident fever (where fever is defined as an oral temperature  $\geq 38.5^{\circ}\text{C}$ ).
3. Grade 4 thrombocytopenia lasting more than 7 consecutive days.
4. A platelet count  $< 10,000/\text{mm}^3$  at any time.
5. Greater than or equal to Grade 3 thrombocytopenia with clinically significant bleeding.
6. Greater than or equal to Grade 3 nonhematological toxicity, with the following exceptions:
  - Grade 3 or greater nausea or emesis, or both, that occurs in the absence of optimal antiemetic therapy (5-HT<sub>3</sub> serotonin receptor antagonist).
  - Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy with loperamide.
  - Grade 3 fatigue that lasts less than 1 week.
  - Grade 3 nonhematological toxicity that can be controlled to Grade 2 or less with appropriate treatment (eg, Grade 3 hypertension will be considered a DLT only if the hypertension is unmanageable by standard approved pharmacological agents or if symptomatic sequelae are identified despite appropriate medical intervention).
7. Greater than or equal to Grade 2 nonhematological toxicities that are considered by the investigator to be related to study drug and in the opinion of the investigator require dose reduction.

8. Delay in the initiation of the subsequent cycle of therapy by more than 10 days due to treatment-related toxicity.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment during the dose escalation part of this study will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels or alternative schedules.

Patients experiencing DLTs in Cycle 1 may continue in the study provided they are deriving clinical benefit but will have doses of alisertib and/or paclitaxel reduced as appropriate.

#### **6.4 Dose Escalation Rules**

The dose escalation will follow the 3 + 3 traditional rules and dose intervals will follow the outline provided in [Table 6-1](#). Should more data be needed to better understand the observed safety and/or PK, with the agreement of the sponsor's project clinician (or designee), cohort(s) at any dose level may be expanded. Intrapatient dose escalation is not planned and will not be permitted in this study. Patients who do not meet the DLT-evaluable criteria in the dose-escalation part of the study will be replaced.

Accrual and treatment will proceed according to the following rules:

1. The initial cohort will start with the treatment of 3 patients at DL1 (15-mg BID alisertib):
  - If 0 of 3 patients experience a DLT, dose escalation will proceed to the next planned dose level (DL2 / 25-mg BID alisertib), at which 3 patients will be enrolled.
  - If 1 of 3 patients experiences a DLT, 3 more patients will be enrolled at that same dose level. Escalation will continue if no more than 1 of 6 patients experiences a DLT.
  - If 2 or more patients experience DLT at DL1, depending on the overall safety profile and the type of AEs/DLTs observed, a decision will be made to either expand the 15-mg BID alisertib cohort with 6 additional patients, to de-escalate the alisertib dose to 10 mg BID (DL-1), or to terminate the study. In the case of an expansion of the DL1 cohort, a tolerable dose will then require first-cycle DLTs in no more than 3 out of 12 DLT-evaluable patients to confirm MTD.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

2. At DL2 (25-mg BID alisertib):

- If 0 of 6 patients experience a DLT AND if alisertib exposures in the combination setting in the East Asian population are unexpectedly lower than anticipated from single-agent experience in East Asian patients, the alisertib dose may be escalated further following discussion between the investigator and the sponsor.
- MTD declaration will require first-cycle DLTs in no more than 1 out of 6 DLT evaluable patients
- If 2 of 6 patients experience a DLT, alisertib will be de-escalated and an intermediate dose level of alisertib 20 mg BID (DL3-intermediate) will be explored.

3. At DL3 (20-mg BID alisertib)

- MTD declaration will require first cycle DLTs in no more than 1 out of 6 DLT evaluable patients.
- If 2 or more of 6 patients experience a DLT, alisertib will be de-escalated to the DL1 (15-mg BID alisertib) and 3 additional patients will be enrolled at that dose level if there are not yet 6 patients enrolled.

The RP2D regimen will be established following evaluation of the available data from the dose escalation portion of the trial which will include, but is not limited to, DLTs, toxicity characterization (Grade 3/4 AEs, SAEs, toxicities leading to early dose reduction and treatment discontinuation). For the purpose of the RP2D regimen, Cycle 1 PK data from 6 evaluable patients will be used in addition to the available clinical data. AEs that meet DLT criteria in Cycle 2 and beyond will not necessarily influence dose escalation but will be considered when determining the RP2D regimen. Following discussions between the sponsor and the investigators, expansion of an existing dose level to confirm the safety of the dosing regimen is permissible if the nature of the DLTs and AEs allows further exploration. Upon review of available data and agreement on the RP2D by the sponsor and investigators, enrollment in the expansion portion of the study may begin. The dose expansion part of the study will further investigate the safety and tolerability of the RP2D that was determined during dose escalation.

**Table 6-1 Alisertib Combined With Paclitaxel for Phase 1 Dose Escalation**

<b>Cohort</b>	<b>Target Alisertib (PO) Dose and Schedule</b>	<b>Target Paclitaxel (IV) Dose and Schedule</b>
<b>Starting Dose Level</b>		
1	15 mg BID for 3 days on/4 days off repeated weekly $\times 3$ weeks in 28-day cycle	60 mg/m <sup>2</sup> on Days 1, 8, 15
2	25 mg BID for 3 days on/4 days off repeated weekly $\times 3$ weeks in 28-day cycle	60 mg/m <sup>2</sup> on Days 1, 8, 15
3-intermediate	20 mg BID for 3 days on/4 days off repeated weekly $\times 3$ weeks in 28-day cycle	60 mg/m <sup>2</sup> on Days 1, 8, 15
-1	10 mg BID for 3 days on/4 days off repeated weekly $\times 3$ weeks in 28-day cycle	60 mg/m <sup>2</sup> on Days 1, 8, 15

Abbreviations: IV = intravenous; PO = orally, by mouth.

## **6.5 Dose-Modification Guidelines**

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective as of 14 June 2010. These criteria are provided in the Study Manual and are available online at [ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html).

**NOTE:** Dose reductions for all events are permanent and should be for all subsequent cycles (ie, once a dose has been reduced, it cannot be re-escalated to a higher dose).

### **6.5.1 Criteria for Beginning a Subsequent Treatment Cycle**

For a new cycle of therapy to begin the following criteria must be met:

- ANC must be  $\geq 1,500/\text{mm}^3$
- Platelet count must be  $\geq 75,000/\text{mm}^3$
- All other toxicity considered by the investigator to be related to therapy with alisertib (except alopecia) or paclitaxel must have resolved to  $\leq$  Grade 1, or to a level considered acceptable by the physician, or to the patient's baseline values before a new cycle of therapy may begin.
- There has been a minimum rest period of 11 days and a maximum of 21 days since the last dose of study drug.

### **6.5.2 Criteria for Dose Interruption During a Cycle**

If a patient experiences any of the following toxicities during the dosing period, dosing will be discontinued for the remainder of that cycle, or until recovery sufficient for completion of the cycle or the start of a new treatment cycle.

- Grade 3 neutropenia ( $\text{ANC} \leq 1,000 \text{ cells/mm}^3$ )
- Febrile neutropenia
- Grade 3 thrombocytopenia (platelet count  $< 50,000/\text{mm}^3$ )
- Greater than or equal to Grade 3 nonhematological toxicity, with the following exceptions:
  - Grade 3 or greater nausea, emesis, or both that occurs in the absence of optimal antiemetic therapy (5-HT<sub>3</sub> serotonin receptor antagonist)
  - Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy with loperamide
  - Grade 3 nonhematological toxicity that can be controlled to Grade 2 or less with appropriate treatment (eg, Grade 3 hypertension only if the hypertension is manageable by standard approved pharmacological agents)
- Greater than or equal to Grade 2 nonhematological toxicities that are considered by the investigator to be related to study drug and in the opinion of the investigator require dose interruption

Once the criteria for retreatment (Section 6.5) have been met ( $\text{ANC} > 1000/\text{mm}^3$ , platelet count  $> 50,000/\text{mm}^3$ ), the patient may resume therapy for completion of the cycle. If the Day 8 or Day 15 doses of paclitaxel and alisertib (or paclitaxel alone if applicable) have been delayed through 2 additional days or less (eg, Monday delayed to Wednesday, but restart possible on Thursday), dosing should resume after the delay without omitting doses, and without dose reduction. The subsequent dose of the cycle should preserve the same minimal days between doses within the cycle originally planned; thus, if the planned Day 8 dose is delayed but restarted on Thursday, then the next planned “Day 15” dose would be administered on the following Thursday to preserve a 7-day period between the Day 8 and Day 15 doses.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

If the Day 8 or Day 15 doses of paclitaxel and alisertib have been delayed through additional days due to lack of adequate recovery (eg, dosing originally planned for Monday delayed through Thursday, and restart only possible on Friday or later), both the paclitaxel dose and the 3 associated alisertib doses should be omitted within that cycle. If the doses started on Day 15 are omitted, the cycle should preserve a minimum 2-week treatment-free period between the last dose of protocol treatment and the start of the new cycle. When paclitaxel and alisertib are resumed, either on Day 15 or with the subsequent cycle, the doses of paclitaxel and/or alisertib should be modified with incremental reductions if appropriate (see Section 6.5.3).

### **6.5.3 Dose Modifications**

Patients who continue to experience any toxicity (hematologic or nonhematologic) of a severity that requires additional dose reductions after 1 dose reduction of paclitaxel and 1 dose reduction of alisertib, given administration of appropriate supportive care, should discontinue protocol treatment. However, if the patient has evidence of clinical benefit and would be considered to benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review and written approval by the project clinician. These circumstances should be discussed on a case-by-case basis.

As a general rule, if a patient requires dose reduction due to a study drug-related toxicity, the drug dose may not be re-escalated. Similarly, if a patient requires elimination of alisertib on the last 3 days (Days 15, 16, and 17) (Table 6-2), as described previously, alisertib will only be dosed on the earlier cycle days as planned for all subsequent cycles.

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

**Paclitaxel:** 10-mg/m<sup>2</sup> increment reductions from planned starting dose, administered on Cycle Days 1, 8, and 15. An option for an additional dose reduction (40 mg/m<sup>2</sup>) may be possible in some situations described in the following.

**Alisertib:** Either a 5-mg reduction from planned starting dose, administered on Cycle Days 1 through 3, 8 through 10, and 15 through 17, or an omission of doses on Days 15 through 17, depending on the circumstance for adjustment (Table 6-2), with the option for further dose reduction in some situations described in the following.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

The decision regarding which study drug requires dose reduction will be dependent upon the toxicity, its onset, and time course. For example, neuropathy has been related to paclitaxel, but it has not been a frequent or dominant toxicity associated with alisertib. Although somnolence can be observed from multiple causes in patients with advanced malignancy, it has been observed in some patients as a toxicity associated with high individual doses of alisertib, typically within the first few days of drug administration. Thus, the dose of paclitaxel alone will be adjusted for dose-limiting nonhematologic toxicities such as neuropathy, and the dose of alisertib alone will be reduced for dose-limiting nonhematologic toxicities such as somnolence that is not due to other comorbidities.

Paclitaxel or alisertib will be individually reduced for dose-limiting hematologic toxicities that are attributable to both agents, such as sustained Grade 4 neutropenia, thrombocytopenia, or febrile neutropenia according to [Table 6-2](#). As a general approach to manage these hematologic toxicities which are also attributable to the taxane, paclitaxel should be first delayed and/or reduced before initiation of myeloid growth factors or before modification of alisertib, if applicable. To manage dose-limiting neutropenia attributable to paclitaxel alone or to the combination with alisertib, the general goal is to avoid reducing alisertib dosing below a range considered to be clinically relevant. Given these considerations, the first intervention will be dose reduction of paclitaxel by  $10 \text{ mg/m}^2$ . The next intervention would be to add myeloid growth factor if appropriate. Only after intervention with myeloid growth factor, if appropriate, and in a situation of a repeat occurrence within dosing would the alisertib be reduced by 5 mg/dose. In the situation of a repeat occurrence of hematological toxicity after completion of dosing in a cycle, the last 3 days of alisertib or placebo would be omitted. If the treating physician (or investigator) believes that at a particular occurrence and due to the nature of the event or patient history, an intervention treatment that deviates from the described general guidelines is preferred, it should be discussed with and approved by the sponsor's project clinician (or designee).

Prophylactic use of myeloid growth factors are not allowed for patients newly enrolled who receive the first cycle, but may be administered for supportive care to manage neutropenia events if clinically indicated, according to American Society of Clinical Oncology (ASCO) guidelines and/or institutional practices. Thus, myeloid growth factors are not mandated, but if used per investigator discretion, they should be administered according to local guidelines, the product label, and [Table 6-2](#). During the first cycle of patients enrolled to the dose escalation part, the use of myeloid growth factors should be avoided unless DLT or dose interruption criteria have already been met. Short acting myeloid growth factors are

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

preferred, and they should be discontinued for an appropriate number of days before restart of protocol treatment.

Alternative dose modifications may be recommended after discussion with the investigator and project clinician/designee to maximize exposure of study treatment while protecting patient safety.

**Table 6-2 Dose Modification Rules: Hematological Toxicity**

<b>Alisertib + Paclitaxel</b>	
First occurrence	Reduce paclitaxel 1 level (eg, 60 mg/m <sup>2</sup> to 50 mg/m <sup>2</sup> )
Repeat occurrence	Add myeloid growth factor without further dose modification, if appropriate <sup>a</sup>
Repeat occurrence within dosing period (Days 1-17)	Reduce alisertib 1 level (ie, a 5-mg reduction) <sup>a</sup>
Or	
Repeat occurrence after dosing complete, during treatment-free period (Days 18-28)	Omit alisertib in last 3 days of schedule (ie, Days 15, 16, and 17) but maintain the same alisertib doses for Days 1-3 and 8-11 as administered on earlier cycles
Repeat occurrence	Discontinue <sup>b</sup> Paclitaxel 40 mg/m <sup>2</sup> AND/OR Alisertib with 1 dose reduction level, omitting Days 15-17

Abbreviations: BID = twice daily.

a The use of myeloid growth factors is not mandated but is strongly encouraged as an intervention step for neutropenia before dose reduction of alisertib or further dose reduction of paclitaxel if appropriate.

b A patient may continue the protocol with further dose reductions (hematologic and nonhematologic toxicities) if he or she is deriving clinical benefit, upon review and written approval by the project clinician. The actual doses to be administered in those situations are listed. The decision to reduce only 1 of the agents or both should be based on similar considerations regarding the type of adverse event at this time. Note: If after the first occurrence, the myeloid growth factor was not an option, the patient may continue the protocol with myeloid growth factor, if appropriate, before discontinuation.

No more than 1 dose reduction of paclitaxel will be allowed. However, if the patient has clinical benefit and would benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review and written approval by the project clinician.

**Dose Modifications for Nonhematologic Toxicities**

- Dose modifications with incremental reductions will be as described previously for hematologic toxicities; however, only the drug thought to be responsible for the toxicity should be reduced. If both alisertib and paclitaxel may have contributed, or

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

the investigator is uncertain which drug is responsible, then dose modification will be as described above for hematologic toxicities starting with paclitaxel (first occurrence).

- For both the “within” and “after” dosing regimens at the next repeat occurrence with dose modified, drug will be discontinued but with the option to continue under the considerations detailed in the last row of [Table 6-2](#). Specific dose adjustment is required for oral mucositis ([Table 6-3](#)).

**Table 6-3 Dose Adjustments for Oral Mucositis (Drug-related)**

Toxicity	NCI CTCAE Grade	Finding	Action on Drug
<b>Mucositis oral</b>	Grade 1	Asymptomatic or mild symptoms; intervention not indicated	Medical management as appropriate, no action on study drug.
	Grade 2	Moderate pain; not interfering with oral intake; modified diet indicated	<ul style="list-style-type: none"> <li>Medical management as appropriate.</li> <li>Hold alisertib until resolution to Grade <math>\leq 1</math> or baseline but pursue paclitaxel as single agent at current dose level.</li> </ul>
	Grade 3	Severe pain; interfering with oral intake	<p>Upon recovery (at any time during the cycle), resume alisertib at current dose level.</p> <ul style="list-style-type: none"> <li>Hold paclitaxel and alisertib.</li> <li>Upon recovery to Grade <math>\leq 2</math>, resume paclitaxel only at current dose level.</li> </ul>
	Grade 4	Life-threatening consequences; urgent intervention indicated	Upon recovery to Grade $\leq 1$ or baseline (at any time during the cycle), resume alisertib at the next lower dose level.
Lack of acceptable timely recovery	<b>Delay <math>&gt; 21</math> days in the start of a subsequent cycle</b> due to lack of recovery of oral mucositis to Grade 2 for initiation of paclitaxel and/or Grade 1 for initiation of alisertib	Discontinue study drug.	Discontinue study drug. The maximum delay before treatment should be discontinued is 3 weeks (Section 6.3.1).

• Abbreviation: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**Suggested Management of Stomatitis**

Stomatitis/oral mucositis/mouth ulcers should be treated using local supportive care. In addition to standard oral and dental assessment and hygiene, please consider the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

**1. PROPHYLAXIS:**

- Consider prophylaxis with salt water (0.9%) mouthwash or baking soda (1 teaspoon per glass of warm water) 2 to 3 times per day to prevent mucositis starting the day of alisertib for up to 7 days thereafter.

**2. ESTABLISHED STOMATITIS:**

- For mild toxicity (Grade 1), use conservative measures such as nonalcoholic mouthwash, artificial saliva, or salt water (0.9%) mouthwash 4 to 6 times daily until resolution. Limit to foods that do not require significant chewing, and avoid acidic, salty, or dry foods.
- For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), use topical analgesic mouth treatments (eg, local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase<sup>®</sup>).

**3. AGENTS THAT SHOULD BE AVOIDED:**

- Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mucositis and should be avoided.

**6.6 Excluded Concomitant Medications and Procedures**

The following medications and procedures are prohibited during the study:

- Use of any antineoplastic therapy other than study drug (alisertib or paclitaxel) is not permitted.
- Use of any other investigational therapy is not permitted.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

- Alternative therapy or medicine(s) are not allowed. Palliative radiation therapy for pain management on a lesion not established as progressive and located outside of the field of a target/nontarget lesion is allowed. (Note that radiation therapy should occur during the rest period and not while dosing.)
- Use of any PPI or pancreatic enzyme is prohibited during the conduct of the study and within 5 days before the first dose of alisertib. Patients may be administered alternative agents to manage gastric acidity or reflux (eg, H2 receptor antagonists, antacids) with exceptions described in the following.
  - Histamine 2 receptor antagonists are to be avoided during the alisertib treatment period, but may be used during the rest period if clinically indicated to treat mucositis or other GI abnormalities. Brief administration of histamine-2 antagonists (such as a single dose of cimetidine or ranitidine) is allowed if required on the day of paclitaxel administration.
  - Neutralizing antacids and calcium-containing supplements should be avoided within 2 hours before and 2 hours after alisertib administration.
- Enzyme-inducing drugs such as phenytoin, carbamazepine, phenobarbital, oxcarbazepine, primidone, rifampin, rifabutin, rifapentine, or St. John's wort are not permitted within 14 days before the first dose of alisertib, and the use of these agents is not permitted during the study.
- Use of moderate or strong CYP3A inhibitors is not permitted within 14 days before the first dose of study drug and during the conduct of the study. (see Section [14.2](#))

**6.7 Permitted Concomitant Medications and Procedures**

Myeloid and erythroid growth factors may be used in accordance with the American Society of Clinical Oncology guidelines<sup>(46)</sup> or local institutional policy guidelines. The use of myeloid and erythroid growth factors will be prohibited in the DLT evaluation period as detailed in Section [6.5.3](#). Antiemetic agents may be administered at the discretion of the investigator.

Anticoagulation is permitted; however, the risks for bleeding in the setting of low platelets should be carefully assessed. Platelet counts may require more frequent monitoring per

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

clinical practice standards, and doses of anticoagulants should be adjusted or held in the setting of thrombocytopenia to mitigate the risk of bleeding.

Medications with potential CNS effects are not prohibited in this study, but it is recommended that their use be minimized to avoid confusion in the interpretation of CNS effects should they occur during the course of treatment with alisertib. Because of structural and pharmacological similarity between alisertib and benzodiazepines, concomitant therapy with benzodiazepines is discouraged but not prohibited.

Premedication with corticosteroids, diphenhydramine, or histamine-2 receptor antagonists is permitted before each treatment with paclitaxel.

All other medical conditions should be treated at the discretion of the investigator in accordance with local community standards of medical care.

## **6.8 Precautions and Restrictions**

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

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 30 days after the last dose of study drug, see details in the following.

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, see details in the following.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

<b>Barrier Methods (each time the subject has intercourse)</b>	<b>Intrauterine Devices (IUDs)</b>	<b>Hormonal Contraceptives</b>
<ul style="list-style-type: none"><li>• Male condom PLUS spermicide</li><li>• Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide</li><li>• Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide</li></ul>	<ul style="list-style-type: none"><li>• Copper T PLUS condom or spermicide</li><li>• Progesterone T PLUS condom or spermicide</li></ul>	<ul style="list-style-type: none"><li>• Implants</li><li>• Hormone injections</li><li>• Combined pills</li><li>• Minipills</li><li>• Patches</li><li>• Vaginal ring PLUS male condom and spermicide</li></ul>

Patients must adhere to any treatment-specific pregnancy prevention guidelines for paclitaxel

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study. Patients should also become familiar with the effects of the study drugs before engaging in such activities.

Patients are to be instructed to limit the use of alcohol while enrolled in this study. Patients should consume no more than 1 standard unit of alcohol per day during the study and for 30 days after the last dose of study drug. A standard unit of alcohol is defined as 12 ounces of beer (350 mL), 1.5 ounces (45 mL) of 80-proof alcohol, or one 6-ounce (175 mL) glass of wine.

## **6.9 Management of Clinical Events**

### **6.9.1 Nausea and Vomiting**

Prophylactic antiemetic therapy may be used in this study per standard of care. If prophylactic antiemetic therapy is needed, 5-HT<sub>3</sub> receptor antagonists should be tried first. Because of the potential for benzodiazepines to cause sedation, the use of benzodiazepines for anti-emetic prophylaxis should be reserved for patients who cannot be satisfactorily managed otherwise.

There is no prohibition against anti-emetic use in the management of a patient who develops nausea or vomiting, or both.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**6.9.2 Diarrhea**

Antidiarrheal medications will not be used prophylactically; however, patients will be instructed to take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, patients may take 4 mg of loperamide every 4 hours. Fluid intake should be maintained to avoid dehydration.

**6.9.3 Central Nervous System Effects**

If a patient experiences excessive sedation believed to be related to alisertib, treatment with alisertib should be interrupted. Patients whose sedation is not considered immediately life-threatening should be carefully monitored and given appropriate supportive care.

**6.9.4 Hypersensitivity Reactions Associated With Paclitaxel**

Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of paclitaxel therapy. Severe reactions, however, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel. Please refer to the paclitaxel product label for further information.

**6.10 Blinding and Unblinding**

This is an open-label study.

**6.11 Description of Investigational Agents**

Alisertib drug product is supplied as the ECT dosage form in 10- and 15-mg strength, with dose strength expressed as the milligrams of active drug (free acid). CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Paclitaxel will be supplied as a solution for injection in a 100 mg/16.7 mL vial labeled as investigational material.

## **6.12 Preparation, Reconstitution, and Dispensation**

Alisertib ECT are packaged in a 60-cc high-density polyethylene (HDPE) bottle with a rayon coil, induction seal, desiccant packs, and a polypropylene child-resistant cap.

Please refer to the paclitaxel product label for instructions and precautions regarding preparation and handling.

Alisertib and paclitaxel are anticancer drugs, and as with other potentially toxic compounds, caution should be exercised when handling alisertib and paclitaxel. It is recommended that gloves and protective clothing be worn during preparation.

## **6.13 Packaging and Labeling**

The packaged and labeled study drug, alisertib ECT, will be provided by Millennium and will be handled at the investigative site as open-label material. The labels on the study drug will fulfill all requirements specified by governing regulations. Alisertib will be supplied as ECT in 10- or 15-mg strength. The 60-cc HDPE bottles will have a child-resistant cap and be labeled for take-home use. Patients will receive instructions for home use of alisertib, including the requirement that alisertib be administered as intact tablets.

Paclitaxel will be labeled as investigational material and provided to the investigative site by Millennium; packaging labels will fulfill all requirements specified by governing regulations. Paclitaxel will be supplied as a solution for injection in a 100 mg/16.7 mL vial (6 mg/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.

## **6.14 Storage, Handling, and Accountability**

Tablets should remain in the bottle provided until use. The container should be stored at the investigative site at controlled room temperature (20°C to 25°C; 68°F to 77°F; excursions permitted from 15°C to 30°C; 59°F to 86°F) and used before the retest expiry date provided by Millennium. The stability of the drug product will be monitored for the duration of the clinical studies. Tablets are not intended to be broken or manipulated in any way.

Containers should be kept closed during storage.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

Because alisertib is an investigational agent, it should be handled with due care. In case of contact with broken tablets, raising dust should be avoided during the cleanup operation.

The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during the cleanup operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken tablet), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes.

In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients are to be instructed on proper storage, accountability, and administration of alisertib, including that alisertib is to be taken as intact tablets.

Vials of paclitaxel should be stored at 20°C to 25°C (68°F to 77°F), protected from light. Please refer to the paclitaxel product label for further information regarding the proper storage and handling of paclitaxel.

Procedures for drug accountability at the investigational site are described in Section [10.10](#).

## **6.15 Other Protocol-Specified Materials**

This section is not applicable.

## **7. STUDY CONDUCT**

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

### **7.1 Study Personnel and Organizations**

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

## **7.2 Arrangements for Recruitment of Patients**

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

## **7.3 Treatment Group Assignments**

Patient accrual and treatment is discussed in Section [6.4](#)

## **7.4 Study Procedures**

Refer to the [Schedule of Events](#) for timing of assessments. Additional details are provided as necessary in the sections that follow.

### **7.4.1 Informed Consent**

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

### **7.4.2 Patient Demographics**

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

### **7.4.3 Medical History**

During the Screening period (within 28-days before the first dose of any study drug), a complete medical history will be obtained and a complete physical examination, including neurological examination, performed. Additionally, concomitant medications will be listed and will include all medications being taken at the time of screening and within 28 days of the first dose.

### **7.4.4 Physical Examination**

A physical examination will be completed per standard of care at the times specified in the [Schedule of Events](#).

The screening physical examination will include the patient's height (Section [7.4.5](#)) and weight (Section [7.4.5](#)) and will also include an assessment of the patient's ECOG performance status (see Section [14.1](#)).

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

The symptom-directed physical examination will be performed at Cycle 1, Day 1 (baseline), and within 3 days before the beginning of each treatment cycle (Day 1) and on Days 8, 15, and 21 of each treatment cycle. In patients who tolerate study treatment through multiple cycles, the Day 21 symptom-directed physical examination can become optional, at the discretion of the investigator, if in the prior 2 cycles the patient tolerated study treatment (ie, without the requirement for dose reduction or without  $\geq$  Grade 3 treatment-related toxicity evaluated according to NCI CTCAE, version 4.03). For patients who have been on study for longer than 6 months and/or have discontinued paclitaxel treatment, the Day 8 and Day 15 physical examinations are optional, at the discretion of the investigator.

The Cycle 1, Day 1 (baseline) symptom-directed physical examination is not required if the screening medical history was obtained and the screening complete physical examination was conducted within the 4 days before administration of the Cycle 1, Day 1 dose of study drug.

During the symptom-directed physical examination, neurotoxicity will be monitored through AE reporting and concomitant medication usage.

The symptom-directed physical examination will be repeated at the End of Treatment (EOT) visit (see [Schedule of Events](#)). The symptom-directed physical examination will be directed toward the identification of new symptoms and signs, and changes in concomitant medications (Section [7.4.8](#)).

#### **7.4.5 Patient Height and Weight**

Height will be measured during screening only (within 28 days before the first dose of any study drug).

Weight will be measured during screening; at Cycle 1, Day 1 (baseline); and within 3 days before the beginning (Day 1) of each subsequent treatment cycle.

If the screening assessment was done within 4 days before Cycle 1, Day 1, an assessment at Cycle 1, Day 1 is not necessary.

Weight also will be measured at the EOT visit.

#### **7.4.6 Vital Signs**

Vital signs (systolic and diastolic blood pressures, heart rate, and temperature) measurements will be obtained during screening; at Cycle 1, Day 1 (baseline); within 3 days

before the beginning of each treatment cycle (Day 1); and on Days 8, 15, and 21 of each treatment cycle. If the screening assessment was done within 4 days before Cycle 1, Day 1, an assessment at Cycle 1, Day 1 is not necessary. During Screening and Cycle 1, temperature should be oral measurements only; temperature measurements in all other cycles may be taken based on local practice.

For patients who have been on study for longer than 6 months and/or have discontinued paclitaxel treatment, the Day 8 and Day 15 vital sign assessments are optional, at the discretion of the investigator.

Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

Vital signs measurements also will be obtained at the EOT visit.

#### **7.4.7      Pregnancy Test**

A serum beta-human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test will be performed only for patients of childbearing potential during screening and again at Cycle 1, Day 1 (baseline) if the screening test was performed more than 4 days before the first dose of alisertib or paclitaxel. The results must be negative within 4 days before the first dose of alisertib or paclitaxel is administered (ie, within the 4 days prior to Cycle 1, Day 1), or as otherwise required by local regulations.

Additional pregnancy testing may be performed during the study at the discretion of the investigator, as per request of IEC/IRB, or if required by local regulations.

If a patient becomes pregnant or suspects pregnancy while participating in this study, the investigator must be informed immediately (see Section 9.4).

Women of childbearing potential will be defined as sexually mature females who meet the following criteria:

1. Those who have not undergone hysterectomy or bilateral oophorectomy, and
2. Those who have not had natural menopause (eg, FSH  $> 40$  IU/L and no menstrual period for at least 24 consecutive months) for 24 consecutive months or longer (loss of menstrual periods following chemotherapy may not rule out childbearing potential).

#### **7.4.8 Concomitant Medications and Procedures**

Concomitant medications and supportive therapies will be recorded from 28 days before the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first. Medications with potential CNS effects are not prohibited in this study, but it is recommended that their use be minimized to avoid confusion in the interpretation of CNS effects should they occur during the course of treatment with alisertib. Because of alisertib's structural and pharmacological similarity to the benzodiazepines, concomitant therapy with benzodiazepines is discouraged but not prohibited. See Section 6.6 and Section 6.7 for a list of excluded and permitted concomitant medications and procedures, respectively.

#### **7.4.9 Adverse Events**

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

#### **7.4.10 Enrollment**

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

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

#### **7.4.11 Electrocardiogram**

A 12-lead ECG will be obtained at screening and at Cycle 1, Day 1 (baseline). If the screening ECG was obtained within the 4 days before the Cycle 1, Day 1 dose of study drug, a repeat ECG at Cycle 1, Day 1 is not necessary. Additional ECGs may be obtained if clinically indicated. Electrocardiogram assessments are to be performed with the patient supine and rested for 5 minutes and before any closely timed blood collection.

#### **7.4.12 Clinical Laboratory Evaluations**

Blood samples for analysis of the following hematology and clinical chemistry parameters, and urine for urinalysis will be obtained as specified in the [Schedule of Events](#). Clinical laboratory evaluations will be performed by local laboratories. Handling and shipment of clinical laboratory samples will be outlined in the Study Manual. Clinical laboratory evaluations will be performed as outlined in the following.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

If screening values were obtained and acceptable within the 4 days before the Cycle 1, Day 1 dose of study drug, repeat clinical laboratory testing (hematology, clinical chemistry, or urinalysis) at Cycle 1, Day 1 is not necessary.

A blood sample for hematology (complete blood count [CBC] with differential white blood cell [WBC] count) will be obtained during screening; within 3 days before the beginning (Day 1) of each treatment cycle; and on Day 8 (- 2 days), Day 15 (- 2 days), and Day 21 (- 2 days). In patients who tolerate study treatment through multiple cycles, the Day 21 clinical laboratory assessments can become optional, at the discretion of the investigator, if in the prior 2 cycles the patient tolerated study treatment (ie, without the requirement for dose reduction or without  $\geq$  Grade 3 treatment-related toxicity evaluated according to NCI CTCAE, version 4.03). If a patient has an ANC less than 500/mm<sup>3</sup> or a platelet count less than 25,000/mm<sup>3</sup>, or both, the CBC with differential should be repeated at least every 2 to 3 days until the ANC or platelet count (or both, if both were decreased) have exceeded these values on at least 2 occasions.

For patients who have been on study for longer than 6 months and/or have discontinued paclitaxel treatment, the Day 8 and Day 15 clinical laboratory assessments are optional, at the discretion of the investigator.

A blood sample for CBC with differential also will be obtained at the EOT visit.

**Hematology**

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

A blood sample for clinical chemistry panel will be obtained during screening, within 3 days before the beginning (Day 1) of each treatment cycle, and at the EOT visit.

**Serum Chemistry**

- Blood urea nitrogen (BUN)
- Albumin
- Creatinine
- Alkaline phosphatase (ALP)
- Bilirubin (total)
- Aspartate aminotransferase (AST)
- Urate
- Alanine aminotransferase (ALT)
- Lactate dehydrogenase (LDH)
- Calcium
- Chloride
- Carbon dioxide (CO<sub>2</sub>) if available
- Magnesium

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

- Gamma glutamyl transferase (GGT)
- Phosphate
- Glucose
- Sodium
- Potassium

Thyroid stimulating hormone (TSH) level will be measured at screening or Cycle 1, Day 1 (baseline) and at the EOT visit; this test should be repeated during the treatment period as clinically indicated.

A urine sample for urinalysis will be obtained during screening, at Cycle 1, Day 1 (baseline), and at the EOT visit.

### **Urinalysis**

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

If urine protein by dipstick changes to 3+ (or 2+ that is reconfirmed at least 1 day later), then a 24-hour urine collection should be done for protein and creatinine clearance. The screening or Cycle 1, Day 1 urinalysis should include microscopic examination of the sediment.

#### **7.4.13 CA-125 Assessment**

For patients with ovarian, fallopian tube, or peritoneal cancer, CA-125 levels will be obtained according to standard of care within 9 days before screening and sufficient time after prior therapy, or within the Screening period; and within 4 days before the dose on Cycle 1, Day 1; and at the end of every treatment cycle (within the week before the start of a new treatment cycle); and at the EOT visit. The investigator's determination of response by CA-125 is required at the end of every 2 cycles. Please refer to the Gynecological Cancer Intergroup guideline for the Definition of CA-125 response.<sup>(47)</sup>

#### **7.4.14 HBV and HCV Assessment**

At screening assessments, HBV surface antigen, HBV core antibody, and HCV antibody testing are mandatory. If HBcAb is positive, HBV DNA should be assessed. If HCVAb is positive, HCV-RNA should be tested.

For patients who are HBcAb positive screening, DNA titers will be taken every 2 months.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

- If DNA titers increase (1 log increase of viral load), treat with antivirals medication (lamivudine) and continue monitoring.
- If a second 1 log of increase of viral load occurs, stop treatment and discontinue from the study.

#### **7.4.15 Disease Assessment**

Patients will undergo computed tomography (CT) with contrast as appropriate, magnetic resonance imaging (MRI), x-ray and/or bone scanning to monitor and assess disease progression, using RECIST criteria (version 1.1).<sup>(48)</sup> Contrast CT scans of the chest, abdomen, and pelvis will be obtained at screening. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation using an imaging modality consistent with that used at screening. Objective assessments will be performed at each time point as described in the [Schedule of Events](#). When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents.

Repeat CT (with IV contrast) or MRI scans as appropriate, or both, are to be performed at the completion of Cycle 2 and every 2 cycles (approximately every 8 weeks, between Days 21 and 28 of every even cycle) thereafter until PD is documented. The same imaging modality should be used throughout the study for each site of disease. For responders, radiographic images will be read locally but will be collected and, if necessary, provided to the sponsor for subsequent review. Scans are required at the EOT visit only if PD has not been documented previously and it has been 8 weeks or more since the previous evaluation.

Other procedures, such as physical examinations and other scintigraphic examinations (eg, bone scans for patients with known or suspected bone metastases) should be taken into consideration also when evaluating the extent of malignant disease.

In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**7.4.16 Tumor Biopsies (Not Applicable)**

**7.4.17 Pharmacokinetic Measurements**

Paclitaxel PK measurements will be performed on Day 1 of Cycle 1 (weekly paclitaxel dosed during concomitant administration of alisertib) and on Day 1 of Cycle 2 (weekly paclitaxel administered alone). Blood samples for the measurement of plasma concentrations of paclitaxel will be collected at prespecified time points on Day 1 of both Cycles 1 and 2 (see also [Alisertib and Paclitaxel PK Sampling Schedule](#)).

**7.4.17.2 Alisertib Pharmacokinetic Measurements**

Blood samples to measure plasma concentrations of alisertib will be collected at prespecified time points on Days 1 and 3 of Cycle 1 (see also the [Alisertib and Paclitaxel PK Sampling Schedule](#)).

**7.4.18 Pharmacodynamic Measurements (Not Applicable)**

**7.5 Completion of Treatment**

Treatment with alisertib is to be considered completed for patients meeting any of the following criteria:

- 12 months of treatment
- PD (see below for exception)
- Symptomatic deterioration

A patient can be treated for up to 12 months. If it is determined that a patient tolerates protocol treatment and would derive benefit from continued alisertib treatment beyond 12 months, alisertib treatment may be continued in this or in another extension or rollover study, if available, upon request by the investigator and agreement by the project clinician.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

A patient who experiences PD, as defined by imaging results described in the protocol (Section 14.4) may continue protocol treatment if tolerated and if the investigator determines it is in the patient's best interest upon review and agreement by the project clinician.

Criteria for removing patients from the study include the following:

1. Patients with unequivocal evidence of any new metastasis including development of peritoneal studding or malignant ascites must be removed from the study.
2. Patients whose disease progression is such that they are at risk for catastrophic complications from vital organ compression (eg, spinal cord compression, small bowel obstruction, encroachment of major blood vessels, etc) must be removed from the study immediately and treated appropriately.
3. Patients with evidence of progression based on RECIST must be removed from the study if the subsequent assessment (8 weeks later) demonstrates evidence of progressive disease.
4. Patients must be informed of the evidence of progression and the availability of alternative treatments.

In addition to the previous criteria, patients who have PD that is symptomatic or leads to altered organ function, such as increases in bilirubin by 1 common terminology criteria severity grade that could represent altered drug clearance, should be removed from study.

**7.6 Completion of Study**

Patients will be considered to have completed the study if they complete 1 year of treatment with alisertib plus paclitaxel.

**7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement**

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

- Adverse event
- Protocol violation
- Complete response
- Progressive disease

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

- Symptomatic deterioration
- Unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Use of antineoplastic therapy other than study drug (alisertib or paclitaxel)
- Other

Once study drug has been discontinued, all study procedures outlined for the End of Treatment visit will be completed as specified in the [Schedule of Events](#). The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who are withdrawn from treatment during Cycle 1, either for reasons other than DLT, or because they do not meet DLT-evaluable criteria, will be replaced.

Patients who withdraw from the study for any reason may continue with alternative doses or schedules of taxane therapy at the discretion of the treating physician.

## **7.8      Withdrawal of Patients From Study**

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

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- Completed study
- Death
- Other
- Complete response

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

- Progressive disease
- Initiation of subsequent antineoplastic therapy

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. However, every effort will be made to follow all patients for safety.

### **7.9 Study Compliance**

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing, including the following: applicable lot numbers and total drug administered in milligrams (mg). Any discrepancy regarding the dose administered and the reason for the discrepancy will be noted in the eCRF.

Paclitaxel will be administered by study personnel.

Patients will receive a sufficient quantity of alisertib for each treatment cycle. The study center staff will check the patient's diary versus the patient's supply of remaining alisertib tablets at the Day 8, Day 15, and Day 21 visit of each treatment cycle and at the EOT visit to ensure proper compliance with dosing. For patients who do not require a clinic visit on Day 21, the medication count may be confirmed verbally with the patient by telephone; however, a check of the patient diary versus the patient's supply of alisertib tablets should be performed at the next visit (eg, on Day 1 of the subsequent cycle or at the EOT visit, if applicable). Patients who are not compliant with the dosing schedule may be withdrawn from the study.

## **8. STATISTICAL AND QUANTITATIVE ANALYSES**

### **8.1 Statistical Methods**

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. Summary tabulations will be presented displaying 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 will be developed and finalized before database lock.

### **8.1.1 Determination of Sample Size**

During the study, different doses of alisertib are planned for evaluation when combined with a fixed dose of paclitaxel to identify the RP2D. Dose escalation will be conducted according to a traditional dose escalation rule, with 3 to 6 patients evaluated at each dose level. There will be an expansion cohort at the RP2D to at least 12 patients. Including 10% of patients who are not evaluable for DLT, it is anticipated that enrollment of approximately 30 patients is needed.

### **8.1.2 Randomization and Stratification**

There is no randomization or stratification; all patients will receive alisertib plus weekly paclitaxel.

### **8.1.3 Populations for Analysis**

The populations used for analysis will include the following:

- Safety population: The safety population, defined as all patients who receive at least 1 dose of any study drug, will be used for all safety analyses.
- PK population: The PK population, defined as all patients who have sufficient dosing data and plasma concentration-time data to permit calculations of PK parameters, will be used for PK analyses.
- DLT-evaluable population: the DLT-evaluable population, defined as all patients who either experience DLT during Cycle 1 or complete treatment with at least 15 of the planned 18 doses of alisertib and 2 of the planned 3 doses of paclitaxel in Cycle 1 unless AE/DLTs and have sufficient follow up data to allow the investigators and sponsor to determine whether DLT occurred, will be used for analysis of DLT.

### **8.1.4 Procedures for Handling Missing, Unused, and Spurious Data**

All available data will be included in data listings. No imputation of values for missing data will be performed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

### **8.1.5 Demographic and Baseline Characteristics**

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, race, ethnicity, and other parameters, as appropriate.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**8.1.6 Efficacy Analysis**

There is no primary efficacy endpoint in the study.

The secondary efficacy endpoint in the expansion part of the study is the disease response based on the RECIST version 1.1 ORR (CR + PR), which will be presented in a listing.

**8.1.7 Pharmacokinetics/Pharmacodynamics/Biomarkers**

**Pharmacokinetic Analysis**

**Paclitaxel**

Individual and mean plasma concentration data (grouped by alisertib dose level) will be plotted over time for paclitaxel alone (Cycle 2, Day 1) and for paclitaxel administered concomitantly with alisertib (Cycle 1, Day 1). Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters, including, but not limited to,  $C_{max}$ ,  $AUC_{0-t_{last}}$ ,  $AUC_{0-inf}$ , and  $t_{1/2}$ , for paclitaxel administered alone (Cycle 2, Day 1) and during concomitant administration of alisertib (Cycle 1, Day 1). Descriptive statistics will be presented for plasma PK parameters grouped by alisertib dose level. Additionally, the ratio of geometric means of paclitaxel  $C_{max}$ ,  $AUC_{0-t_{last}}$ , and  $AUC_{0-inf}$  (when administered with the MTD/RP2D of alisertib in reference to when administered alone) and the associated 90% CI will be calculated.

**Alisertib**

Individual and mean plasma concentration-time data will be plotted for alisertib on Days 1 and 3 by dose level. Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters of alisertib, including but not limited to, Day 1 and Day 3  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-\infty}$ . Alisertib plasma concentration-time data and PK parameters will be summarized descriptively by dose level using the PK-evaluable population.

**Pharmacodynamic Analysis**

This is not applicable to this study.

**Biomarkers**

This is not applicable to this study.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**8.1.8 Safety Analysis**

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

Safety evaluations will be based on the incidence, intensity, and type of AEs; and clinically significant changes in the patient's vital signs, weight, and clinical laboratory results. Safety variables will be tabulated and presented for the safety population. The incidence of DLT will be presented. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization. All AEs occurring on study will be listed in data listings. Treatment-emergent AEs will be tabulated, where treatment-emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug. AEs are to be tabulated using MedDRA system organ class, high-level term, and preferred term, including the following treatment-emergent 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
- Treatment-emergent AEs resulting in study drug discontinuation
- SAEs

The most commonly reported treatment-emergent AEs (ie, those events reported by  $\geq 10\%$  of all patients in the safety population) will be tabulated by the MedDRA 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.

Clinical laboratory parameters will be summarized at each scheduled time point. Shift tables will be produced for selected laboratory parameters. These tables will summarize the

number of patients with each baseline NCI CTCAE grade and changes to the worst NCI CTCAE grade during study.

Descriptive statistics for the actual values of vital signs and weight over time will be tabulated by scheduled time point.

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

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

### **8.1.9      Interim Analysis**

There is no formal interim analysis.

## **9.      ADVERSE EVENTS**

### **9.1      Definitions**

#### **9.1.1      Pretreatment Event Definition**

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

#### **9.1.2      Adverse Event Definition**

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

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

### **9.1.3      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.<sup>(1)</sup> 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<sup>3</sup> to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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

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

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

### **SAE Reporting Contact Information**

PPD

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial *or* before study drug was given are not to be

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

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.<sup>(1)</sup> The criteria are provided in the Study Manual.

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

### **9.3 Monitoring of Adverse Events and Period of Observation**

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

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

### **9.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events**

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study

drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 9.2). The pregnancy must be followed for the final pregnancy outcome.

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

## **10. ADMINISTRATIVE REQUIREMENTS**

### **10.1 Good Clinical Practice**

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

### **10.2 Data Quality Assurance**

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

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

### **10.3 Electronic Case Report Form Completion**

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

**Alisertib (MLN8237)  
Clinical Study Protocol C14022 Amendment 01**

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.

**10.4 Study Monitoring**

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

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

**10.5 Ethical Considerations**

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

## **10.6 Patient Information and Informed Consent**

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

## **10.7 Patient Confidentiality**

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

## **10.8 Investigator Compliance**

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

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

## **10.9 On-site Audits**

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

## **10.10 Investigator and Site Responsibility for Drug Accountability**

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

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

## **10.11 Product Complaints**

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact <sup>PPD</sup> (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**  
**(US and International)**

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 Cognizant (refer to Section 9.2).

## **10.12 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

**Alisertib (MLN8237)  
Clinical Study Protocol C14022 Amendment 01**

- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

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

#### **10.13 Record Retention**

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

### **11. USE OF INFORMATION**

All information regarding alisertib 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 alisertib and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

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.

The Millennium clinical pharmacologist will be the lead and corresponding author on abstracts and publications of the data generated from this study; the overall principal investigator or lead enroller will be the last author. Subsequently, individual investigators may publish results from their study center in compliance with their agreements with Millennium. Millennium reserves the right to determine which authors are named on abstracts and publications and also reserves the right to determine the order in which named authors appear.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**12. INVESTIGATOR AGREEMENT**

I have read Protocol C14022 Amendment 01: A Phase 1b Study of Alisertib (MLN8237) in Combination With Weekly Paclitaxel in East Asian 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)

**13. REFERENCES**

1. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. 2010 14 June 2010.
2. Chen W. Biochemical characterization of MLN8237 inhibition of Aurora A. Cambridge, MA: Millennium Pharmaceuticals; 2007. Report No.: RPT-00932.
3. Ecsedy J. MLN8237 inhibition of Aurora A and Aurora B in cultured human tumor cells. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2007. Report No.: RPT-00927.
4. Ecsedy J, Bembenek M. Activity of MLN8237 against a kinase selectivity panel. Cambridge (MA, USA): Millennium Pharmaceuticals, Inc.; 2009. Report No.: RPT-00956, Amendment No. 2.
5. Giet R, Glover DM. Drosophila aurora B kinase is required for histone H3 phosphorylation and condensin recruitment during chromosome condensation and to organize the central spindle during cytokinesis. *Journal of Cell Biology* 2001;152(4):669-82.
6. Littlepage LE, Wu H, Andresson T, Deanehan JK, Amundadottir LT, Ruderman JV. Identification of phosphorylated residues that affect the activity of the mitotic kinase Aurora-A. *Proceedings of the National Academy of Sciences of the United States of America* 2002;99(24):15440-5.
7. LeRoy P. Effects of MLN8237 on the proliferation of cultured human tumor cells. Cambridge, (MA, USA): Millennium Pharmaceuticals, Inc.; 2009. Report No.: RPT-00928, Amendment 2.
8. Giet R, McLean D, Descamps S, Lee MJ, Raff JW, Prigent C, et al. Drosophila Aurora A kinase is required to localize D-TACC to centrosomes and to regulate astral microtubules. *Journal of Cell Biology* 2002;156(3):437-51.
9. Honda R, Korner R, Nigg EA. Exploring the functional interactions between Aurora B, INCENP, and survivin in mitosis. *Molecular Biology of the Cell* 2003;14(8):3325-41.
10. Marumoto T, Hirota T, Morisaki T, Kunitoku N, Zhang D, Ichikawa Y, et al. Roles of aurora-A kinase in mitotic entry and G2 checkpoint in mammalian cells. *Genes to Cells* 2002;7(11):1173-82.
11. Hirota T, Kunitoku N, Sasayama T, Marumoto T, Zhang D, Nitta M, et al. Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. *Cell* 2003;114(5):585-98.

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

12. Hoar K, Chakravarty A, Rabino C, Wysong D, Bowman D, Roy N, et al. MLN8054, a small-molecule inhibitor of Aurora A, causes spindle pole and chromosome congression defects leading to aneuploidy. *Molecular & Cellular Biology* 2007;27(12):4513-25.
13. Keen N, Taylor S. Aurora-kinase inhibitors as anticancer agents. *Nature Reviews. Cancer* 2004;4(12):927-36.
14. Ecsedy J. In vivo antitumor activity of MLN8237 administered orally to mice bearing human tumor xenografts. Cambridge (MA, USA): Millennium Pharmaceuticals, Inc.; 2010. Report No.: RPT-01174, Amendment 3.
15. Manfredi M. In vivo anti-tumor activity of MLN8237 given orally in female NCR nude mice bearing human colorectal carcinoma xenografts. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2007. Report No.: RPT-00925, Amendment 1.
16. Nickerson C, Zhang M, Huck J. In vivo antitumor activity of MLN8237 given alone or in combination with rituximab in disseminated models of human diffuse large B cell lymphomas grown in immunocompromised mice. Cambridge (MA, USA): Millennium Pharmaceuticals, Inc.; 2009. Report No.: RPT-01173, Amendment 1.
17. Zhang M. In vivo anti-tumor activity of MLN8237 given orally in female NCR nude mice bearing human lung xenografts. Cambridge (MA, USA): Millennium Pharmaceuticals, Inc.; 2009. Report No.: RPT-00926, Amendment 2.
18. Zhang M. In vivo antitumor activity of MLN8237 given alone or in combination with rituximab in models of human diffuse large b-cell lymphomas grown subcutaneously in immunocompromised mice. Cambridge (MA, USA): Millennium Pharmaceuticals, Inc.; 2011. Report No.: RPT-01245.
19. Pediatric preclinical testing program (PPTP) evaluation of the Aurora A kinase inhibitor MLN8237 [package insert]. San Diego, CA: 2008.
20. Carol H, Boehm I, Reynolds CP, Kang MH, Maris JM, Morton CL, et al. Efficacy and pharmacokinetic/pharmacodynamic evaluation of the Aurora kinase A inhibitor MLN8237 against preclinical models of pediatric cancer. *Cancer Chemother Pharmacol* 2011;68(5):1291-304.
21. Zhang M. Pharmacokinetic/pharmacodynamic/efficacy relationship of MLN8237 in female NCR nude mice bearing the HCT-116 human colorectal carcinoma xenograft. Cambridge, (MA, USA): Millennium Pharmaceuticals, Inc.; 2009. Report No.: RPT-00939, Amendment 2.
22. Silverman L. The acute central nervous system pharmacologic profile of MLN8237-004 following oral administration in Sprague-Dawley rats. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2007. Report No.: RPT-00950.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

23. Doherty C. A cardiovascular assessment of MLN8237-004 following oral administration to conscious, radio-telemetry-instrumented male beagle dogs. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2007. Report No.: RPT-01010.
24. Padgett E. A repeat dose toxicity study of MLN8237-004 when administered via oral gavage in the Sprague-Dawley rat. Ashland, OH: WIL Research Laboratories, LLC; 2007. Report No.: WIL-416032, Amendment 2.
25. Eapen A. A repeat dose oral toxicity study of MLN8237-004 when administered via oral gavage in the beagle dog. Ashland, OH: WIL Research Laboratories, LLC; 2007. Report No.: WIL-416033, Amendment 1.
26. Padgett EL. A 6-month (6-cycle) toxicity study of MLN8237-004 administered via oral gavage with a 28-day recovery period in Sprague-Dawley rats. Ashland (OH, USA): WIL Research Laboratories, LLC; 2010. Report No.: WIL-416086.
27. Eapen AK. A 6-month (6-cycle) toxicity study of MLN8237-004 administered via oral gavage with a 28-day recovery period in beagle dogs. Ashland (OH, USA): WIL Research Laboratories, LLC; 2010. Report No.: WIL-416087.
28. Doherty C. In vitro binding study of MLN8237 to the hERG channel in HEK-293 cells. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2006. Report No.: RPT-00931.
29. Weissman A. Customized screening program prepared for Millennium Pharmaceuticals. Hanover (MD): NovaScreen; 2006. Report No.: T/O 06-2709.
30. Warner SL, Munoz RM, Stafford P, Koller E, Hurley LH, Von Hoff DD, et al. Comparing Aurora A and Aurora B as molecular targets for growth inhibition of pancreatic cancer cells. *Molecular Cancer Therapeutics* 2006;5(10):2450-8.
31. Wells M. MLN8237 Salmonella-E. coli/Mammalian microsome reverse mutation assay. Evanston, IL: Midwest BioResearch, LLC; 2006. Report No.: MBR06-228.
32. Hurley J. MLN8237: An oral (gavage) bone marrow micronucleus test in female Sprague Dawley rats. Ashland, OH: WIL Research Laboratories, LLC; 2011. Report No.: WIL-416109.
33. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. Cancer incidence and incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Japanese Journal of Clinical Oncology* 2014;44(4):388-96.
34. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. *Lancet* 2011;378(9804):1741-55.
35. Sorensen M, Pijls-Johannesma M, Felip E. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v120-5.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

36. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *European Journal of Cancer* 2010;46(4):765-81.
37. Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. *European Respiratory Journal* 2010;35(1):202-15.
38. Yamamoto N, Tsurutani J, Yoshimura N, Asai G, Moriyama A, Nakagawa K, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. *Anticancer Research* 2006;26(1B):777-81.
39. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. *British Journal of Cancer* 1998;77(2):347-51.
40. Stahel R, Thatcher N, Fruh M, Le Pechoux C, Postmus PE, Sorensen JB, et al. 1st ESMO Consensus Conference in lung cancer; Lugano 2010: small-cell lung cancer. *Annals of Oncology* 2011;22(9):1973-80.
41. NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer version 2.2013. 2013 2013.
42. Lin YG, Immaneni A, Merritt WM, Mangala LS, Kim SW, Shahzad MM, et al. Targeting aurora kinase with MK-0457 inhibits ovarian cancer growth. *Clinical Cancer Research* 2008;14(17):5437-46.
43. Anand S, Penrhyn-Lowe S, Venkitaraman AR. AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol. *Cancer Cell* 2003;3(1):51-62.
44. Yang H, He L, Kruk P, Nicosia SV, Cheng JQ. Aurora-A induces cell survival and chemoresistance by activation of Akt through a p53-dependent manner in ovarian cancer cells. *International Journal of Cancer* 2006;119(10):2304-12.
45. Scharer CD, Laycock N, Osunkoya AO, Logani S, McDonald JF, Benigno BB, et al. Aurora kinase inhibitors synergize with paclitaxel to induce apoptosis in ovarian cancer cells. *Journal of Translational Medicine* 2008;6:79.
46. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *Journal of Clinical Oncology* 2006;24(19):3187-205.
47. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *International Journal of Gynecological Cancer* 2011;21(2):419-23.

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

48. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45(2):228-47.
49. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 1982;5(6):649-55.
50. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16(1):31-41.

## **14. APPENDICES**

### **14.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status**

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

Source: Oken MM, et al. 1982.<sup>(49)</sup>

### **14.2 List of Strong and Moderate CYP3A Inhibitors**

#### **Strong CYP3A inhibitor**

Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

#### **Moderate CYP3A inhibitor**

Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

**14.3 Cockcroft-Gault Equation**

For male subjects:

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

For female subjects:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16(1):31-41.<sup>(50)</sup>

**14.4 Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1)**

Disease response will be assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) guidelines, version 1.1.<sup>(48)</sup>

## **14.5 Amendment 1 Detailed Summary of Changes**

---

THE PRIMARY SECTION(S) OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 1 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

---

**Purpose:** Remove visit windows of  $\pm 2$  days from footnotes to remove repetition.

The primary change occurs in the [Schedule of Events](#):

Deleted text: g The Cycle 1, Day 1 (baseline) symptom-directed physical examination is not required if the screening complete physical examination was conducted within the 4 days before administration of the Cycle 1, Day 1 dose of study drug. A symptom-directed physical examination will be repeated within 3 days before the beginning (Day 1) of each new treatment cycle; on Day 8 ( $\pm 2$  days), Day 15 ( $\pm 2$  days), and Day 21 ( $\pm 2$  days) of each treatment cycle; and at the EOT visit.

Sections that also contain this change are:

- [Schedule of Events](#) footnote h
- [Section 7.4.4, Physical Examination](#)
- [Section 7.4.6, Vital Signs](#)

---

**Purpose:** Allow body temperature to be measured according to local practice at study time points other than at Screening and Cycle 1; all Screening and Cycle 1 measurements must be taken orally.

The primary change occurs in [Section 7.4.6, Vital Signs](#):

Formerly read: Vital signs (systolic and diastolic blood pressures, heart rate, and ~~oral~~ temperature) measurements will be obtained during screening; at Cycle 1, Day 1 (baseline); within 3 days before the beginning of each treatment cycle (Day 1); and on Days 8 ( $\pm 2$  days), 15 ( $\pm 2$  days), and 21 ( $\pm 2$  days) of each treatment cycle. If the screening assessment was done within 4 days before Cycle 1, Day 1, an assessment at Cycle 1, Day 1 is not necessary.

---

Now reads: Vital signs (systolic and diastolic blood pressures, heart rate, and temperature) measurements will be obtained during screening; at Cycle 1, Day 1 (baseline); within 3 days before the beginning of each treatment cycle (Day 1); and on Days 8, 15, and 21 of each treatment cycle. If the screening assessment was done within 4 days before Cycle 1, Day 1, an assessment at Cycle 1, Day 1 is not necessary. **During Screening and Cycle 1, temperature should be oral measurements only; temperature measurements in all other cycles may be taken based on local practice.**

The [Schedule of Events](#) also contains this change.

---

**Purpose:** Clarify the timing of CA-125 level assessments (for patients with ovarian cancer).

The primary change occurs in Section [7.4.13, CA-125 Assessment](#):

Formerly read: For patients with ovarian, fallopian tube, or peritoneal cancer, CA-125 levels will be obtained according to standard of care within 9 days before screening and sufficient time after prior therapy within 4 days before the dose on Cycle 1, Day 1; at the end of every treatment cycle; within the week before the start of a new treatment cycle; and at the EOT visit. The investigator's determination of response by CA-125 is required at the end of every 2 cycles.

---

Now reads: For patients with ovarian, fallopian tube, or peritoneal cancer, CA-125 levels will be obtained according to standard of care within 9 days before screening and sufficient time after prior therapy, **or within the Screening period; and** within 4 days before the dose on Cycle 1, Day 1; **and** at the end of every treatment cycle (within the week before the start of a new treatment cycle); and at the EOT visit. The investigator's determination of response by CA-125 is required at the end of every 2 cycles. **Please refer to the Gynecological Cancer Intergroup guideline for the Definition of CA-125 response.**<sup>(47)</sup>

The [Schedule of Events](#) also contains this change.

---

**Purpose:** Clarify the screening requirements for HBV and HCV, and to add details of monitoring for patients who test HBcAb+ at Screening.

The primary change occurs in Section [7.4.14, HBV and HCV Assessment](#):

Added text: **At screening assessments, HBV surface antigen, HBV core antibody, and HCV antibody testing are mandatory. If HBcAb is positive, HBV DNA should be assessed. If HCVAb is positive, HCV-RNA should be tested.**

**For patients who are HBcAb positive screening, DNA titers will be taken every 2 months.**

- **If DNA titers increase (1 log increase of viral load), treat with antivirals medication (lamivudine) and continue monitoring.**
- **If a second 1 log of increase of viral load occurs, stop treatment and discontinue from the study.**

Sections that also contain this change are:

- [Section 5.2, Exclusion Criteria](#) (Criterion #18)
- The [Schedule of Events](#)

---

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

---

**Purpose:** Adjust the requirement for disease evaluation so that patients will be evaluated up to progressive disease.

The primary change occurs in Section [7.4.15, Disease Assessment](#):

Deleted text: Repeat CT (with IV contrast) or MRI scans as appropriate, or both, are to be performed at the completion of Cycle 2 and every 2 cycles (approximately every 8 weeks, between Days 21 and 28 of every even cycle) thereafter ~~for up to 12 months or~~ until PD is documented.

The [Schedule of Events](#) also contains this change.

---

**Purpose:** Clarify that paclitaxel and alisertib should be administered 1 hour apart on Cycle 1, Day 1.

The change occurs in the [Schedule of Events](#):

Formerly read:  
v During Cycle 1, and Cycle 3 and beyond, alisertib dosing will begin on Day 1; subsequent dosing will occur on Days 2, 3, 8, 9, 10, 15, 16, and 17. During Cycle 2 only, alisertib dosing will begin on Day 8 and will continue on Days 9 and 10, and on Days 15, 16, and 17. Refer to [Table 6-1](#) for alisertib dose administration and titration schema. On ~~days~~ when both paclitaxel and alisertib are administered, alisertib should be administered 1 hour before the start of the paclitaxel infusion. Alisertib will be dispensed to the patient on Day 1. ~~Tests and procedures should be performed on schedule, but may be adjusted (+ 2 days) for administrative and safety reasons.~~ If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessment is completed before dosing. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the sponsor/designee clinician.

Now reads:  
w During Cycle 1, and Cycle 3 and beyond, alisertib dosing will begin on Day 1; subsequent dosing will occur on Days 2, 3, 8, 9, 10, 15, 16, and 17. During Cycle 2 only, alisertib dosing will begin on Day 8 and will continue on Days 9 and 10, and on Days 15, 16, and 17. Refer to [Table 6-1](#) for alisertib dose administration and titration schema. On **Cycle 1 Day 1** when both paclitaxel and alisertib are administered, alisertib should be administered 1 hour before the start of the paclitaxel infusion. Alisertib will be dispensed to the patient on Day 1. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessment is completed before dosing. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the sponsor/designee clinician

---

**Purpose:** Allow a longer window for adjusting dosing and study assessments due to safety concerns (+3 days, rather than  $\pm 2$  days, allowed for administrative reasons).

The change occurs in the [Schedule of Events](#):

Added text:  
Each treatment cycle is 28-days in length. Tests and procedures should be done on schedule, but visit windows of  $\pm 2$  days are allowed (except as otherwise specified) occasionally for holidays, vacations, and other administrative reasons. **A dosing windows of + 3 days is allowed due to safety concerns.** If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled assessment within this time frame, the patient may continue in the study only with written permission of the project clinician.

---

**Purpose:** Clarify the timing for the predose paclitaxel PK sample collection on Day 1.

The change occurs in the [Alisertib and Paclitaxel PK Sampling Schedule](#):

Added text: g The predose sample for alisertib PK on Days 1 and 3 can be timed to coincide with the **predose sample for paclitaxel PK on Day 1 and the 47-h paclitaxel PK sample** depending on the timing of alisertib dosing.

---

**Purpose:** Correct errors in percents reported for adverse events in the pooled data from single-agent studies of alisertib.

The change occurs in Section [1.3, Clinical Experience](#):

Formerly read: The more commonly observed ( $\geq 30\%$  incidence) treatment-emergent AEs (TEAEs) from pooled data across the alisertib single-agent studies include **fatigue (48%)**, neutropenia (48%), anemia (45%), diarrhea (42%), alopecia (37%), nausea (32%), and stomatitis (31%).

---

Now reads: The more commonly observed ( $\geq 30\%$  incidence) treatment-emergent AEs (TEAEs) from pooled data across the alisertib single-agent studies include **neutropenia (47%)**, **fatigue (46%)**, anemia (45%), diarrhea (42%), alopecia (35%), nausea (32%), and stomatitis (31%).

---

**Purpose:** Allow for expansion of dose escalation cohort(s) to enable a better understanding of safety and/or PK, if needed.

The change occurs in Section [4.1, Overview of Study Design](#):

Added text: If alisertib exposures in the combination setting in the East Asian population are unexpectedly lower than anticipated from single-agent experience in East Asian patients, and no DLTs have occurred in the DL2 cohort (alisertib 25 mg BID plus 60 mg/m<sup>2</sup> paclitaxel), the alisertib dose may be escalated further following discussion between the investigator and the sponsor pending PK and safety assessment. **Should more data be needed to better understand the observed safety and/or PK, with the agreement of the sponsor's project clinician (or designee), cohort(s) at any dose level may be expanded.** Intrapatient dose escalation will not be permitted in this study. It is planned that at least 1 Japanese patient will be included in each of the dose levels explored.

Sections that also contain this change are:

- [Section 6.4, Dose Escalation Rules](#)
- [Protocol Summary](#)

---

**Purpose:** Clarify that there will be **approximately** 2 to 3 study centers in the escalation part of the study.

The change occurs in Section [4.2, Number of Patients](#):

Added text: There will be **approximately** 2 to 3 study centers in the escalation part and approximately 10 study centers in the expansion part.

---

**Purpose:** Redefine adequate renal function (Inclusion Criterion 8) by either creatinine levels or estimated creatinine clearance.

The change occurs in Section [5.1, Inclusion Criteria](#) (criterion #8):

Added text: Adequate renal function as defined by:

- Creatinine  $< 1.5 \times$  **institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula**  $\geq 30$  mL/minute **for patients with creatinine levels above institutional ULN** (can be calculated using serum creatinine value; see Section [14.3](#)).

---

**Purpose:** Add details to clarify Inclusion Criterion 9 regarding previous chemotherapy regimen allowance.

The change occurs in Section [5.1, Inclusion Criteria](#) (criterion #9):

Formerly read: No more than 2 previous chemotherapy regimen ~~in the metastatic setting~~.

Now reads: **Patients must have received at least 1 prior chemotherapy regimen, but no more than 2 previous chemotherapy regimens for the advanced and/or metastatic stage disease. The neo-adjuvant chemotherapy or post-surgical adjuvant chemotherapy for early-stage disease would be counted.**

---

**Purpose:** Revise Exclusion Criterion 11 to specify that there must be no use of proton pump inhibitors within 5 days (rather than 4 days) of the first dose of alisertib.

The primary change occurs in Section [5.2, Exclusion Criteria](#) (criterion #11):

Formerly read: Requirement for administration of proton pump inhibitor (PPI), H2 antagonist (premedication for paclitaxel allowed), or pancreatic enzymes. Use of any PPI in either continued or intermittent use will be prohibited during the conduct of the study and patients must ~~discontinue any use of PPI within 4 days before~~ the first dose of alisertib.

---

Now reads: Requirement for administration of proton pump inhibitor (PPI), H2 antagonist (premedication for paclitaxel allowed), or pancreatic enzymes. Use of any PPI in either continued or intermittent use will be prohibited during the conduct of the study and patients must **not** use a PPI within **5** days **of** the first

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

---

dose of alisertib.

---

**Purpose:** Revise Exclusion Criterion 19 to specify uncontrolled cardiac arrhythmias.

The primary change occurs in Section [5.2, Exclusion Criteria](#) (criterion #19):

Deleted text: History of myocardial infarction, unstable symptomatic ischemic heart disease, uncontrolled hypertension despite appropriate medical therapy, ~~any ongoing cardiac arrhythmias of Grade 2~~, thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy) within 6 months before receiving the first dose of study drug. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed. Patients with a pacemaker may be enrolled in the study upon discussion with the project clinician.

---

**Purpose:** Add an exclusion criterion (Exclusion Criterion 21) for patients with another malignancy within the past 3 years

The change occurs in Section [5.2, Exclusion Criteria](#) (criterion #21):

Added text: **21. Diagnosed with or treated for another malignancy within 3 years before the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type may be enrolled in the study if they have undergone complete resection and no evidence of active disease is present.**

---

**Purpose:** Add details to the instructions for patients regarding the timing of study medication dosing, and add a statement that the study medication should be swallowed whole and not chewed.

The change occurs in Section [6.1, Study Drug Administration](#):

Added text: Patients will be instructed to take each PO dose of alisertib with 8 ounces (1 cup, 240 mL) of water. The 2 daily doses must be taken at least 6 hours apart. Alisertib should be administered on an empty stomach in **the first 3 days of Cycle 1** (no food from 2 hours before the dose until 1 hour after the dose). **Patients should be instructed to take their alisertib study medication at approximately the same time each day, approximately 12 hours apart (eg, 08:00 and 20:00) but not less than 6 hours apart, and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it before swallowing.**

---

**Purpose:** Revise paclitaxel dosing instructions to specify that the length of paclitaxel infusion on Cycle 1, Day 1 and Cycle 2, Day 1 should be 60 minutes (it must not be less than 60 minutes, but may be up to 70 minutes maximum, where necessary), while paclitaxel should be infused over at least 1 hour (but not more than 90 minutes) at all other dosing time points.

The change occurs in Section [6.2.1, Paclitaxel](#):

Added text: Paclitaxel will be administered as an IV infusion over at least 1 hour (but not more than 90 minutes) with a dose of 60 mg/m<sup>2</sup> on Days 1, 8, and 15 in 28-day cycles. **On Cycle 1, Day 1 and Cycle 2, Day 1, the paclitaxel dose should be administered over 60 minutes (it must not be less than 60 minutes, but may be up to 70 minutes maximum, where necessary).** The paclitaxel dose will remain constant throughout the study. The paclitaxel infusion time is 1 hour; the infusion time may be modified if required after review and agreement by the project clinician. Refer to the paclitaxel product label for further details regarding paclitaxel administration.

Sections that also contain this change are:

- [Schedule of Events](#)
- [Alisertib and Paclitaxel PK Sampling Schedule](#)

---

**Purpose:** Allow prophylactic antiemetics during Cycle 1, and allow modifications to premedications without the requirement for project clinician approval.

The change occurs in Section [6.2.2, Premedication for Paclitaxel-Associated Hypersensitivity or Other Acute Reactions](#):

Deleted text: Premedication to prevent paclitaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. Premedications that may be used in this setting can include: corticosteroid (eg, dexamethasone, as a 20-mg single dose, which can be reduced with subsequent paclitaxel cycles); diphenhydramine; a 5-hydroxytryptamine 3 (5-HT<sub>3</sub>) serotonin receptor antagonist antiemetic administered at its labeled dose (~~but prophylactic antiemetic agents should not be administered in the first cycle of treatment if nausea or vomiting is not observed~~). Benzodiazepines are to be avoided. Brief administration of histamine-2 antagonists (such as a single dose of cimetidine or ranitidine) is allowed if required on the day of paclitaxel administration, but prolonged administration of a histamine-2 antagonist (or any other agent that can alter stomach pH or drug absorption) is to be avoided (see Section [6.6](#)). ~~On days when both alisertib and paclitaxel are administered on the same morning, the alisertib should be administered 1 hour before the start of the paclitaxel infusion.~~ Modifications to paclitaxel administration ~~or to the premedications~~ are allowed upon agreement by the project clinician and will be documented

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

in the electronic case report form (eCRF).

---

**Purpose:** Clarify that thrombocytopenia with clinically significant bleeding is a DLT if it is **greater than or equal to** Grade 3 in the dose-limiting toxicity definitions.

The change occurs in Section [6.3, Definitions of Dose-Limiting Toxicity](#):

Added text: 5. **Greater than or equal to** Grade 3 thrombocytopenia with clinically significant bleeding.

---

**Purpose:** Clarification of actions at DL3 (20-mg BID alisertib).

The change occurs in Section [6.4, Dose Escalation Rules](#):

Added text: 3. **At DL3 (20-mg BID alisertib)**

- **MTD declaration will require first cycle DLTs in no more than 1 out of 6 DLT evaluable patients.**
- **If 2 or more of 6 patients experience a DLT, alisertib will be de-escalated to the DL1 (15-mg BID alisertib) and 3 additional patients will be enrolled at that dose level if there are not yet 6 patients enrolled.**

---

**Purpose:** Specify that PK exposure data will be used to support the determination of the recommended phase 2 dose (RP2D).

The change occurs in Section [6.4, Dose Escalation Rules](#):

Formerly read: The RP2D regimen will be established following evaluation of the available data from the dose escalation portion of the trial which will include, but is not limited to, toxicity characterization (Grade 3/4 AEs, SAEs, toxicities leading to early dose reduction and treatment discontinuation). ~~The RP2D will require first cycle DLTs in no more than 1 in 6 DLT evaluable patients enrolled in a given cohort.~~ For the purpose of the RP2D regimen, Cycle 1 data from 6 evaluable patients will be used in addition to the available clinical data ~~supporting tolerance over multiple treatment cycles~~.

---

Now reads: The RP2D regimen will be established following evaluation of the available data from the dose escalation portion of the trial which will include, but is not limited to, **DLTs**, toxicity characterization (Grade 3/4 AEs, SAEs, toxicities leading to early dose reduction and treatment discontinuation). For the purpose of the RP2D regimen, Cycle 1 PK data from 6 evaluable patients will be used in addition to the available clinical data.

---

**Purpose:** Extend the minimum rest period between cycles from 10 days to at least 11 days and a maximum of 21 days.

The change occurs in Section [6.5.1, Criteria for Beginning a Subsequent Treatment Cycle](#):

Formerly For a new cycle of therapy to begin the following criteria must be met:  
read:

...

- There has been a minimum rest period of ~~10 days or longer~~ since the last dose of study drug.

Now For a new cycle of therapy to begin the following criteria must be met:  
reads:

...

- There has been a minimum rest period of **11 days and a maximum of 21 days** since the last dose of study drug.

---

**Purpose:** Revise the criteria for dose interruption during a cycle.

The change occurs in Section [6.5.2, Criteria for Dose Interruption During a Cycle](#):

Formerly  
read:

- Grade 4 neutropenia ( $ANC \leq 500 \text{ cells/mm}^3$ )
- Febrile neutropenia
- Grade 4 thrombocytopenia (platelet count  $< 25,000/\text{mm}^3$ )
- ~~Grade 3 thrombocytopenia associated with clinically significant bleeding~~

...

Once the criteria for retreatment (Section [6.5](#)) have been met, the patient may resume therapy. If the Day 8 or Day 15 doses of paclitaxel and alisertib (or paclitaxel alone if applicable) have been delayed through 2 additional days or less (eg, Monday delayed to Wednesday, but restart possible on Thursday), dosing should resume after the delay without omitting doses, and without dose reduction. The subsequent dose of the cycle should preserve the same minimal days between doses within the cycle originally planned; thus, if the planned Day 8 dose is delayed but restarted on Thursday, then the next planned “Day 15” dose would be administered on the following Thursday to preserve a 7-day period between the Day 8 and Day 15 doses.

If the Day 8 or Day 15 doses of paclitaxel and alisertib (~~or paclitaxel alone, if applicable~~) have been delayed through additional days due to lack of adequate recovery (eg, dosing originally planned for Monday delayed through Thursday, and restart only possible on Friday or later), both the paclitaxel dose and the 3 associated alisertib doses (~~if applicable~~) should be omitted within that cycle. If the doses started on Day 15 are omitted, the cycle should preserve a minimum 2-week treatment-free period between the last dose of

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

protocol treatment and the start of the new cycle. When paclitaxel and alisertib (if applicable) are resumed, either on Day 15 or with the subsequent cycle, the doses of paclitaxel and/or alisertib should be modified with incremental reductions if appropriate (see Section 6.5.3).

Now  
reads

- Grade 3 neutropenia ( $ANC \leq 1,000$  cells/mm $^3$ )
- Febrile neutropenia
- Grade 3 thrombocytopenia (platelet count  $< 50,000$ /mm $^3$ )

...

Once the criteria for retreatment (Section 6.5) have been met ( $ANC > 1000$ /mm $^3$ , platelet count  $> 50,000$ /mm $^3$ ), the patient may resume therapy **for completion of the cycle**. If the Day 8 or Day 15 doses of paclitaxel and alisertib (or paclitaxel alone if applicable) have been delayed through 2 additional days or less (eg, Monday delayed to Wednesday, but restart possible on Thursday), dosing should resume after the delay without omitting doses, and without dose reduction. The subsequent dose of the cycle should preserve the same minimal days between doses within the cycle originally planned; thus, if the planned Day 8 dose is delayed but restarted on Thursday, then the next planned “Day 15” dose would be administered on the following Thursday to preserve a 7-day period between the Day 8 and Day 15 doses.

If the Day 8 or Day 15 doses of paclitaxel and alisertib have been delayed through additional days due to lack of adequate recovery (eg, dosing originally planned for Monday delayed through Thursday, and restart only possible on Friday or later), both the paclitaxel dose and the 3 associated alisertib doses should be omitted within that cycle. If the doses started on Day 15 are omitted, the cycle should preserve a minimum 2-week treatment-free period between the last dose of protocol treatment and the start of the new cycle. When paclitaxel and alisertib are resumed, either on Day 15 or with the subsequent cycle, the doses of paclitaxel and/or alisertib should be modified with incremental reductions if appropriate (see Section 6.5.3).

---

**Purpose:** Revise the dose modification instructions for dose-limiting hematologic toxicities.

The primary change occurs in Section 6.5.3, **Dose Modifications**:

Formerly read: Patients who continue to experience any toxicity (hematologic or nonhematologic) of a severity that requires additional dose reductions after 1 dose reduction of paclitaxel and 1 dose reduction of alisertib, given administration of appropriate supportive care, should discontinue protocol treatment. However, if the patient has evidence of clinical benefit and would be considered to benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review and

---

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

written approval by the project clinician. These circumstances should be discussed on a case-by-case basis. ~~Similarly, if a patient requires elimination of alisertib on the last 3 days (Days 15, 16, and 17), alisertib will be dosed only on the earlier cycle days as planned for all subsequent cycles (see Table 6-1).~~

As a general rule, if a patient requires dose reduction due to a study drug-related toxicity, the drug dose may not be re-escalated.

.....

Paclitaxel or alisertib will be individually reduced for dose-limiting hematologic toxicities that are attributable to both agents, such as sustained Grade 4 neutropenia, thrombocytopenia, or febrile neutropenia according to **Table 6-2**. As a general approach to manage these hematologic toxicities which are also attributable to the taxane, paclitaxel should be first delayed and/or reduced before initiation of myeloid growth factors or before modification of alisertib, if applicable. To manage dose-limiting neutropenia attributable to paclitaxel alone or to the combination with alisertib, the general goals is to avoid reducing alisertib dosing below a range considered to be clinically relevant. Given the consideration, the first intervention will be dose reduction of paclitaxel by  $10 \text{ mg/m}^2$ . The next recommended intervention would be to add myeloid growth factor ~~without further paclitaxel dose reduction~~. Only after intervention with myeloid growth factor would the alisertib be reduced by 5 mg/dose.

Prophylactic use of myeloid growth factors are not allowed for patients newly enrolled who receive the first cycle, but may be administered for supportive care to manage neutropenia events if clinically indicated, according to American Society of Clinical Oncology (ASCO) guidelines and/or institutional practices. Thus, myeloid growth factors are not mandated, but if used per investigator discretion, they should be administered according to local guidelines, the product label, and **Table 6-2**. During the first cycle of patients enrolled to the dose escalation part, the use of myeloid growth factors should be avoided unless DLT or dose interruption criteria have already been met. Short acting myeloid growth factors are preferred, and they should be discontinued for an appropriate number of days before restart of protocol treatment.

**Table 6-2 Dose Modification Rules: Hematological Toxicity (Greater Than Grade 3)**

<b>Alisertib + Paclitaxel</b>	
First occurrence	Reduce paclitaxel 1 level (eg, $60 \text{ mg/m}^2$ to $50 \text{ mg/m}^2$ )
Repeat occurrence	Add myeloid growth factor without further dose modification, if appropriate <sup>a</sup>

**Alisertib (MLN8237)**  
**Clinical Study Protocol C14022 Amendment 01**

Or

Repeat occurrence within dosing period (Days 1-17)	Reduce alisertib 1 level (ie, a 5-mg reduction) <sup>a</sup>
Repeat occurrence after dosing complete, during treatment-free period (Days 18-28)	Omit alisertib in last 3 days of schedule (ie, Days 15, 16, and 17) but maintain the same alisertib doses for Days 1-3 and 8-11 as administered on earlier cycles
Repeat occurrence	Discontinue <sup>b</sup> Paclitaxel 40 mg/m <sup>2</sup> AND/OR Alisertib with 1 dose reduction level, omitting Days 15-17

Abbreviations: BID = twice daily.

a The use of myeloid growth factors is not mandated but is strongly encouraged as an intervention step for neutropenia before dose reduction of alisertib or further dose reduction of paclitaxel if appropriate.

b A patient may continue the protocol with further dose reductions (hematologic and nonhematologic toxicities) if he or she is deriving clinical benefit, upon review and written approval by the project clinician. The actual doses to be administered in those situations are listed. The decision to reduce only 1 of the agents or both should be based on similar considerations regarding the type of adverse event at this time. Note: If after the first occurrence, the myeloid growth factor was not an option, the patient may continue the protocol with myeloid growth factor, if appropriate, before discontinuation.

**Regimen Modifications for Hematologic Toxicities according to Cycle Day Onset Time**

1. During dosing period (Days 1-17 with the combination of paclitaxel plus alisertib):
  - ~~FIRST OCCURRENCE: Reduce paclitaxel by 10 mg (eg, 60 to 50 mg/m<sup>2</sup>) in future cycles~~
  - ~~REPEAT OCCURRENCE: Myeloid growth factors may be administered, maintaining the same doses of study drug(s), per investigator discretion~~
  - ~~REPEAT OCCURRENCE: Reduce alisertib by 1 level (ie, a 5-mg reduction)~~
2. After dosing period (eg, during the treatment-free period upon recovery):
  - ~~FIRST OCCURRENCE: reduce paclitaxel by 10 mg (eg, 60 to 50 mg/m<sup>2</sup>) in future cycles~~

**Alisertib (MLN8237)****Clinical Study Protocol C14022 Amendment 01**

- ~~REPEAT OCCURRENCE: Myeloid growth factors may be administered, maintaining the same doses of study drug(s), per investigator discretion~~
- ~~REPEAT OCCURRENCE: omit the last 3 days (eg, Days 15, 16, and 17) of alisertib in future cycles but maintain the same alisertib doses administered on earlier cycle days~~

No more than 1 dose reduction of paclitaxel will be allowed. However, if the patient has clinical benefit and would benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review by the project clinician.

Now  
reads:

Patients who continue to experience any toxicity (hematologic or nonhematologic) of a severity that requires additional dose reductions after 1 dose reduction of paclitaxel and 1 dose reduction of alisertib, given administration of appropriate supportive care, should discontinue protocol treatment. However, if the patient has evidence of clinical benefit and would be considered to benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review and written approval by the project clinician. These circumstances should be discussed on a case-by-case basis.

As a general rule, if a patient requires dose reduction due to a study drug-related toxicity, the drug dose may not be re-escalated. **Similarly, if a patient requires elimination of alisertib on the last 3 days (Days 15, 16, and 17) (Table 6-2), as described previously, alisertib will only be dosed on the earlier cycle days as planned for all subsequent cycles.**

...

Paclitaxel or alisertib will be individually reduced for dose-limiting hematologic toxicities that are attributable to both agents, such as sustained Grade 4 neutropenia, thrombocytopenia, or febrile neutropenia according to **Table 6-2**. As a general approach to manage these hematologic toxicities which are also attributable to the taxane, paclitaxel should be first delayed and/or reduced before initiation of myeloid growth factors or before modification of alisertib, if applicable. To manage dose-limiting neutropenia attributable to paclitaxel alone or to the combination with alisertib, the general goal is to avoid reducing alisertib dosing below a range considered to be clinically relevant. Given **these** considerations, the first intervention will be dose reduction of paclitaxel by  $10 \text{ mg/m}^2$ . The next intervention would be to add myeloid growth factor **if appropriate**. Only after intervention with myeloid growth factor, **if appropriate, and in a situation of a repeat occurrence within dosing** would the alisertib be reduced by 5 mg/dose. **In the situation of a repeat occurrence of hematological toxicity after completion of dosing in a cycle, the last 3 days of alisertib or placebo would be omitted. If the treating physician (or investigator) believes that at a particular occurrence and due to the nature of the event or patient**

---

**history, an intervention treatment that deviates from the described general guidelines is preferred, it should be discussed with and approved by the sponsor's project clinician (or designee).**

Prophylactic use of myeloid growth factors are not allowed for patients newly enrolled who receive the first cycle, but may be administered for supportive care to manage neutropenia events if clinically indicated, according to American Society of Clinical Oncology (ASCO) guidelines and/or institutional practices. Thus, myeloid growth factors are not mandated, but if used per investigator discretion, they should be administered according to local guidelines, the product label, and Table 6-2. During the first cycle of patients enrolled to the dose escalation part, the use of myeloid growth factors should be avoided unless DLT or dose interruption criteria have already been met. Short acting myeloid growth factors are preferred, and they should be discontinued for an appropriate number of days before restart of protocol treatment.

**Alternative dose modifications may be recommended after discussion with the investigator and project clinician/designee to maximize exposure of study treatment while protecting patient safety.**

**Table 6-2 Dose Modification Rules: Hematological Toxicity**

	Alisertib + Paclitaxel
First occurrence	Reduce paclitaxel 1 level (eg, 60 mg/m <sup>2</sup> to 50 mg/m <sup>2</sup> )
Repeat occurrence	Add myeloid growth factor without further dose modification, if appropriate <sup>a</sup>
Repeat occurrence within dosing period (Days 1-17)	Reduce alisertib 1 level (ie, a 5-mg reduction) <sup>a</sup>
<b>Or</b>	
Repeat occurrence after dosing complete, during treatment-free period (Days 18-28)	Omit alisertib in last 3 days of schedule (ie, Days 15, 16, and 17) but maintain the same alisertib doses for Days 1-3 and 8-11 as administered on earlier cycles
Repeat occurrence	Discontinue <sup>b</sup> Paclitaxel 40 mg/m <sup>2</sup> AND/OR Alisertib with 1 dose reduction level, omitting Days 15-17

Abbreviations: BID = twice daily.

- a The use of myeloid growth factors is not mandated but is strongly encouraged as an intervention step for neutropenia before dose reduction of alisertib or further dose reduction of paclitaxel if appropriate.
- b A patient may continue the protocol with further dose reductions (hematologic and nonhematologic toxicities) if he or she is deriving clinical benefit, upon review and written approval by the project clinician. The actual doses to be administered in those situations are listed. The decision to reduce only 1 of the agents or both should be based on similar considerations regarding the type of adverse event at this time. Note: If after the first occurrence, the myeloid growth factor was not an option, the patient may continue the

---

protocol with myeloid growth factor, if appropriate, before discontinuation.

No more than 1 dose reduction of paclitaxel will be allowed. However, if the patient has clinical benefit and would benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review **and written approval** by the project clinician.

---

**Purpose:** Add specific dose adjustment requirements due to occurrence of oral mucositis/stomatitis/mouth ulcers.

The change occurs in Section [6.5.3, Dose Modifications:](#)

Formally Dose Modifications for Nonhematologic Toxicities  
read

- Dose modifications will be as described previously for hematologic toxicities; however, only the drug thought to be responsible for the toxicity should be reduced. If both alisertib and paclitaxel may have contributed, or the investigator is uncertain which drug is responsible, then ~~both alisertib and paclitaxel should be modified using the incremental reductions described previously.~~
- ~~If a patient requires dose reduction due to a study drug related toxicity, the drug dose may not be re-escalated. Similarly, if a patient requires elimination of alisertib on the last 3 days (eg, Days 15, 16, and 17) due to DLT, as described previously, alisertib will only be dosed on the earlier cycle days as planned for all subsequent cycles.~~
- ~~REPEAT OCCURRENCES: Patients who continue to experience dose-limiting toxicity (hematologic or nonhematologic) after 1 dose reduction, given administration of appropriate supportive care, should discontinue protocol treatment. However, if the patient has clinical benefit and would benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review by the project clinician.~~

Now Dose Modifications for Nonhematologic Toxicities  
reads:

- Dose modifications **with incremental reductions** will be as described previously for hematologic toxicities; however, only the drug thought to be responsible for the toxicity should be reduced. If both alisertib and paclitaxel may have contributed, or the investigator is uncertain which drug is responsible, then **dose modification will be as described above for hematologic toxicities starting with paclitaxel (first occurrence).**
- **For both the “within” and “after” dosing regimens at the next repeat occurrence with dose modified, drug will be discontinued but with the option to continue under the considerations detailed**

in the last row of **Table 6-2**. Specific dose adjustment is required for oral mucositis (**Table 6-3**).

**Table 6-3 Dose Adjustments for Oral Mucositis (Drug-related)**

Toxicity	NCI CTCAE Grade	Finding	Action on Drug
<b>Mucositis oral</b>	<b>Grade 1</b>	Asymptomatic or mild symptoms; intervention not indicated	Medical management as appropriate, no action on study drug.
	<b>Grade 2</b>	Moderate pain; not interfering with oral intake; modified diet indicated	<ul style="list-style-type: none"> <li>Medical management as appropriate.</li> <li>Hold alisertib until resolution to Grade <math>\leq 1</math> or baseline but pursue paclitaxel as single agent at current dose level.</li> </ul>
	<b>Grade 3</b>	Severe pain; interfering with oral intake	<p>Upon recovery (at any time during the cycle), resume alisertib at current dose level.</p> <ul style="list-style-type: none"> <li>Hold paclitaxel and alisertib.</li> <li>Upon recovery to Grade <math>\leq 2</math>, resume paclitaxel only at current dose level.</li> </ul>
	<b>Grade 4</b>	Life-threatening consequences; urgent intervention indicated	Upon recovery to Grade $\leq 1$ or baseline (at any time during the cycle), resume alisertib at the next lower dose level.
<b>Lack of acceptable timely recovery</b>		Discontinue study drug.	
		Delay $> 21$ days in the start of a subsequent cycle due to lack of recovery of oral mucositis to Grade 2 for initiation of paclitaxel and/or Grade 1 for initiation of alisertib	Discontinue study drug. The maximum delay before treatment should be discontinued is 3 weeks (Section 6.3.1).

**Abbreviation:** NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event

#### **Suggested Management of Stomatitis**

**Stomatitis/oral mucositis/mouth ulcers should be treated using local supportive care. In addition to standard oral and dental assessment and hygiene, please consider the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:**

**1. PROPHYLAXIS:**

- Consider prophylaxis with salt water (0.9%) mouthwash or baking soda (1 teaspoon per glass of warm water) 2 to 3 times per day to prevent mucositis starting the day of alisertib for up to 7 days thereafter.**

**2. ESTABLISHED STOMATITIS:**

- For mild toxicity (Grade 1), use conservative measures such as nonalcoholic mouthwash, artificial saliva, or salt water (0.9%) mouthwash 4 to 6 times daily until resolution. Limit to foods that do not require significant chewing, and avoid acidic, salty, or dry foods.**
- For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), use topical analgesic mouth treatments (eg, local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).**

**3. AGENTS THAT SHOULD BE AVOIDED:**

- Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mucositis and should be avoided.**

---

**Purpose:** Clarify that alternative therapy or medicine(s) are not allowed

The change occurs in Section [6.6, Excluded Concomitant Medications and Procedures](#):

Added      The following medications and procedures are prohibited during the study:  
text:      ...

- Alternative therapy or medicine(s) are not allowed.** Palliative radiation therapy for pain management on a lesion not established as progressive and located outside of the field of a target/nontarget lesion is allowed. (Note that radiation therapy should occur during the rest period and not while dosing.)

**Purpose:** Prohibit the use of pancreatic enzyme during the study.

The change occurs in Section [6.6, Excluded Concomitant Medications and Procedures](#):

Added text: The following medications and procedures are prohibited during the study:

...

- Use of any **PPI or pancreatic enzyme** is prohibited during the conduct of the study. Patients may be administered alternative agents to manage gastric acidity or reflux (eg, H2 receptor antagonists, antacids) with exceptions described in the following.

---

**Purpose:** Permit premedication with corticosteroids, diphenhydramine, or histamine-2 receptor antagonists before each treatment with paclitaxel.

The change occurs in Section [6.7, Permitted Concomitant Medications and Procedures](#):

Added text: **Premedication with corticosteroids, diphenhydramine, or histamine-2 receptor antagonists is permitted before each treatment with paclitaxel.**

---

**Purpose:** Correct the definition of women of childbearing potential.

The primary change occurs in Section [7.4.7, Pregnancy Test](#):

Formerly read: Women of childbearing potential will be defined as sexually mature females who meet the following criteria:

1. Those who have not undergone hysterectomy or bilateral oophorectomy, and
2. Those who have not had natural menopause ~~for 24 consecutive months or longer~~ (eg, FSH > 40 IU/L and no ~~menopausal~~ period for at least 24 consecutive months) (loss of ~~menopausal~~ periods following chemotherapy may not rule out childbearing potential).

---

Now reads: Women of childbearing potential will be defined as sexually mature females who meet the following criteria:

1. Those who have not undergone hysterectomy or bilateral oophorectomy, and
2. Those who have not had natural menopause (eg, FSH > 40 IU/L and no **menstrual** period for at least 24 consecutive months) **for 24 consecutive months or longer** (loss of **menstrual** periods following chemotherapy may not rule out childbearing potential).

**Purpose:** Clarify that radiographic images will be provided to the sponsor **if necessary**.

The change occurs in Section [7.4.15, Disease Assessment](#):

Formerly read	Repeat CT (with IV contrast) or MRI scans as appropriate, or both, are to be performed at the completion of Cycle 2 and every 2 cycles (approximately every 8 weeks, between Days 21 and 28 of every even cycle) thereafter <del>for up to 12 months or</del> until PD is documented. The same imaging modality should be used throughout the study for each site of disease. For responders, radiographic images will be read locally but will be collected and provided to the sponsor for subsequent review. Scans are required at the EOT visit only if PD has not been documented previously and it has been 8 weeks or more since the previous evaluation.
Now reads:	Repeat CT (with IV contrast) or MRI scans as appropriate, or both, are to be performed at the completion of Cycle 2 and every 2 cycles (approximately every 8 weeks, between Days 21 and 28 of every even cycle) thereafter until PD is documented. The same imaging modality should be used throughout the study for each site of disease. For responders, radiographic images will be read locally but will be collected and, <b>if necessary</b> , provided to the sponsor for subsequent review. Scans are required at the EOT visit only if PD has not been documented previously and it has been 8 weeks or more since the previous evaluation.

---

**Purpose:** Clarify when patients who are withdrawn in Cycle 1 should be replaced.

The change occurs in Section [7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement](#):

Added text:	Patients who are withdrawn from treatment during Cycle 1, <b>either</b> for reasons other than DLT, <b>or because they do not meet DLT-evaluable criteria</b> , will be replaced.
----------------	---

---

**Purpose:** Add clarification to DLT evaluable population.

The change occurs in Section [8.1.3, Populations for Analysis](#):

Added text:	<ul style="list-style-type: none"><li>• DLT-evaluable population: the DLT-evaluable population, defined as all patients who either experience DLT during Cycle 1 or complete treatment with at least 15 of the planned 18 doses of alisertib and 2 of the planned 3 doses of paclitaxel in Cycle 1 <b>unless AE/DLTs</b> and have sufficient follow up data to allow the investigators and sponsor to determine whether DLT occurred, will be used for analysis of DLT.</li></ul>
----------------	---

**Purpose:** Update the TEAE definition to the current template.

The change occurs in Section [8.1.8, Safety Analysis](#).

Deleted text: AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization. All AEs occurring on study will be listed in data listings. Treatment-emergent AEs will be tabulated, where treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, ~~any event that is considered by the investigator to be drug related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug related~~. AEs are to be tabulated using MedDRA system organ class, high-level term, and preferred term, including the following treatment-emergent categories:

---

**Purpose:** Remove final study analysis description from interim analysis section.

The change occurs in Section [8.1.9, Interim Analysis](#):

Deleted text: There is no formal interim analysis. ~~The final analyses for the CSR will be conducted after all patients enrolled in the study have completed study treatment and follow-up visits. There will be an ongoing review of safety data with the medical monitor and study investigators.~~

---

**Purpose:** Remove administrative language regarding study closure that was intended for a European regulatory system, and is not applicable to this study.

The change occurs in Section [10.12, Closure of the Study](#):

Deleted text: ~~Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.~~  
~~Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.~~  
...  
~~Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.~~

---

**Purpose:** Correct typographical errors, punctuation, grammar, and formatting

These changes are not listed individually.

---

Amendment 1 – A Phase 1b Study of Alisertib (MLN8237) in Combination With Weekly Paclitaxel in East Asian Patients With Advanced Solid Tumors

**ELECTRONIC SIGNATURES**

<b>Signed by</b>	<b>Meaning of Signature</b>	<b>Server Date (dd-MMM-yyyy HH:mm)</b>
PPD	Clinical Approval	15-Jun-2015 18:36
	Clinical Science Approval	25-Jun-2015 12:51