Title: A Multiarm, Open-label, Phase 1b Study of MLN2480 (an Oral A-, B-, and CRAF Inhibitor) in Combination With MLN0128 (an Oral mTORC 1/2 Inhibitor), or Alisertib (an Oral Aurora A Kinase Inhibitor), or Paclitaxel, or Cetuximab, or Irinotecan in Adult Patients With Advanced Nonhematologic Malignancies

NCT Number: NCT02327169

Protocol Approve Date: February 8, 2018

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

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

CLINICAL STUDY PROTOCOL C28002 Amendment 6

MLN2480

A Multiarm, Open-label, Phase 1b Study of MLN2480 (an Oral A-, B-, and CRAF Inhibitor) in Combination With MLN0128 (an Oral mTORC 1/2 Inhibitor), or Alisertib (an Oral Aurora A Kinase Inhibitor), or Paclitaxel, or Cetuximab, or Irinotecan in Adult Patients With Advanced Nonhematologic Malignancies

Protocol Number:	C28002
Indication:	Advanced nonhematologic malignancies
Phase:	1b
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2014-003340-12
Therapeutic Area:	Oncology

Protocol History

Original	07 October 2014
Amendment 1	05 March 2015
Amendment 2	30 June 2015
Amendment 3	31 August 2015
Amendment 4	29 June 2016
Amendment 5 (France only)	22 November 2016
Amendment 6	08 February 2018

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Approved by:

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

PPD

Rationale for Amendment 6

This document describes the changes in reference to the protocol incorporating Amendment 6. The primary reason for this amendment is to define the patient population for enrollment in the Arm 6 expansion cohort of TAK-580 given as monotherapy every other day in patients with non–small-cell lung cancer (NSCLC) and non-V600 BRAF mutations. This is a population that does not respond to currently available V600 BRAF inhibitors and so remains underserved.

Specifically, with this amendment, all patients enrolled into the Arm 6 expansion cohort will be required to have metastatic NSCLC harboring BRAF non-V600 mutations.

It has been estimated that between 3% and 5% of patients with NSCLC harbor BRAF mutations. Approximately half of these mutations are in the V600 site, and the rest are non-V660E mutations [1-4]. Other data have estimated the incidence of BRAF mutations in NSCLC as being as high as 7%, with 70% non-V600 mutations [5]. Although this is a relatively small population, it is comparable to populations of patients with NSCLC that harbor ALK and ROS mutations, for which novel pharmaceutical agents have been successfully developed. Most these patients have adenocarcinomas. It should be mentioned that not every non-V600 mutation may be a driver mutation, and some may not be actionable.

Vemurafenib, a BRAF inhibitor, was tested in a cohort of 20 patients with BRAF mutations (90% of whom harbored V600 mutations) as part of a basket clinical trial [6]. In 19 evaluable patients, 42% had a partial response, and 42% had stable disease, for a clinical benefit rate of 84%. The median progression-free survival was 7.3 months, and the 12-month survival was 66%.

The combination of dabrafenib and trametinib was tested in 93 patients with V600 BRAF mutations; 57 were previously treated, and 36 were treatment naïve. The objective response rate was 63% in the previously treated group and 61% in the treatment-naïve group. The median duration of response was 12.6 months in the previously treated group and had not been reached in the treatment-naïve group. Responses lasting longer than 6 months were seen in 64% and 59% in the previously treated and treatment-naïve patients, respectively [7]. This combination recently received regulatory approval for the treatment of patients with NSCLC and V600 BRAF mutations.

Currently available BRAF inhibitors, however, are ineffective against non-V600 mutations, and there is an interesting scientific explanation for this. The V600 mutation acts via a monomer of the abnormal kinase, and current BRAF inhibitors are capable of inhibiting this enzyme. However, several of the non-V600 mutations act by forming heterodimers with CRAF, and the currently available BRAF inhibitors are not capable of inhibiting this activation. However, as a pan-RAF inhibitor, MLN2480 has the ability to inhibit these heterodimers formed between the mutant BRAF and normal CRAF dimer and could, therefore, have activity in non-V600 mutant BRAF tumors.

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

For specific descriptions of text changes and where the changes are located, see Section 14.5.

Changes in Amendment 6

1. Add a cohort of patients with NSCLC and non-V600 BRAF mutations.
2. Add inclusion criterion 19, which defines the population eligible for enrollment into the Arm 6 expansion cohort as patients with BRAF non-V600 mutation-positive NSCLC.
3. Revise exclusion criterion 15 to include the new Arm 6 expansion cohort.

PROTOCOL SUMMARY

Study Title: A Multiarm, Open-label, Phase 1b Study of MLN2480 (an Oral A-, B-, and CRAF Inhibitor) in Combination With MLN0128 (an Oral mTORC 1/2 Inhibitor), or Alisertib (an Oral Aurora A Kinase Inhibitor), or Paclitaxel, or Cetuximab, or Irinotecan in Adult Patients With Advanced Nonhematologic Malignancies

Number of Patients: Approximately 125

Objectives

Primary

- To determine the safety profile and the maximum tolerated doses (MTDs)/potential recommended phase 2 doses (RP2Ds) of the combination treatments of MLN2480 + MLN0128, MLN2480 + alisertib, MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan in patients with advanced nonhematologic malignancies
- To determine the safety profile and RP2Ds of the combination treatments of MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan

Secondary

- To characterize plasma PK of MLN2480 + MLN0128, MLN2480 + alisertib, MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan upon co-administration in each combination setting
- To evaluate preliminary efficacy as measured by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)

Exploratory

- CCI [redacted]

Study Design Overview: This is an open-label, multicenter, phase 1b study that incorporates a Dose Escalation (Escalation) phase and a Dose Expansion (Expansion) phase. The study will enroll adult patients with advanced, solid (nonhematologic) malignancies and who, in the opinion of the treating physician, have failed standard therapies and for whom a phase 1 trial is an appropriate option.

The Escalation phase will investigate 5 combination arms (ie, MLN2480 + MLN0128, MLN2480 + alisertib, MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan). This study is the first to administer these combinations to humans. Once the MTD for each combination treatment arm has been established, up to 3 combination treatment arms and one monotherapy arm will be evaluated in the Expansion phase based on tolerability and exposure data collected during the Escalation phase. The combination of MLN2480 + paclitaxel will be administered to patients with KRAS exon 2 or BRAF non-V600 mutation-positive non-small cell lung cancer (NSCLC) who are naïve to previous treatment with RAF or MEK inhibitors. The combinations of MLN2480 + cetuximab and MLN2480 + irinotecan will be administered to patients with colorectal cancer (CRC). The combination of MLN2480 + cetuximab will enroll patients with specifically BRAF V600 or non-canonical RAS mutation-positive disease. Non-canonical RAS mutations include KRAS or NRAS non-exon 2 (exon 3 or 4 mutations) or NRAS exon 2 mutated disease. MLN2480 monotherapy will be administered to patients with NSCLC and non-V600 BRAF mutations.

The safety and tolerability of the combination treatment arms will be evaluated using physical examination findings, the incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs), assessment of clinical laboratory values, electrocardiogram (ECG) changes, vital sign measurements, Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory parameters.

Serial blood samples to measure plasma concentrations of MLN2480 and the respective combination agents (not including the MLN2480 monotherapy arm) will be collected during Cycle 1 at prespecified time points.

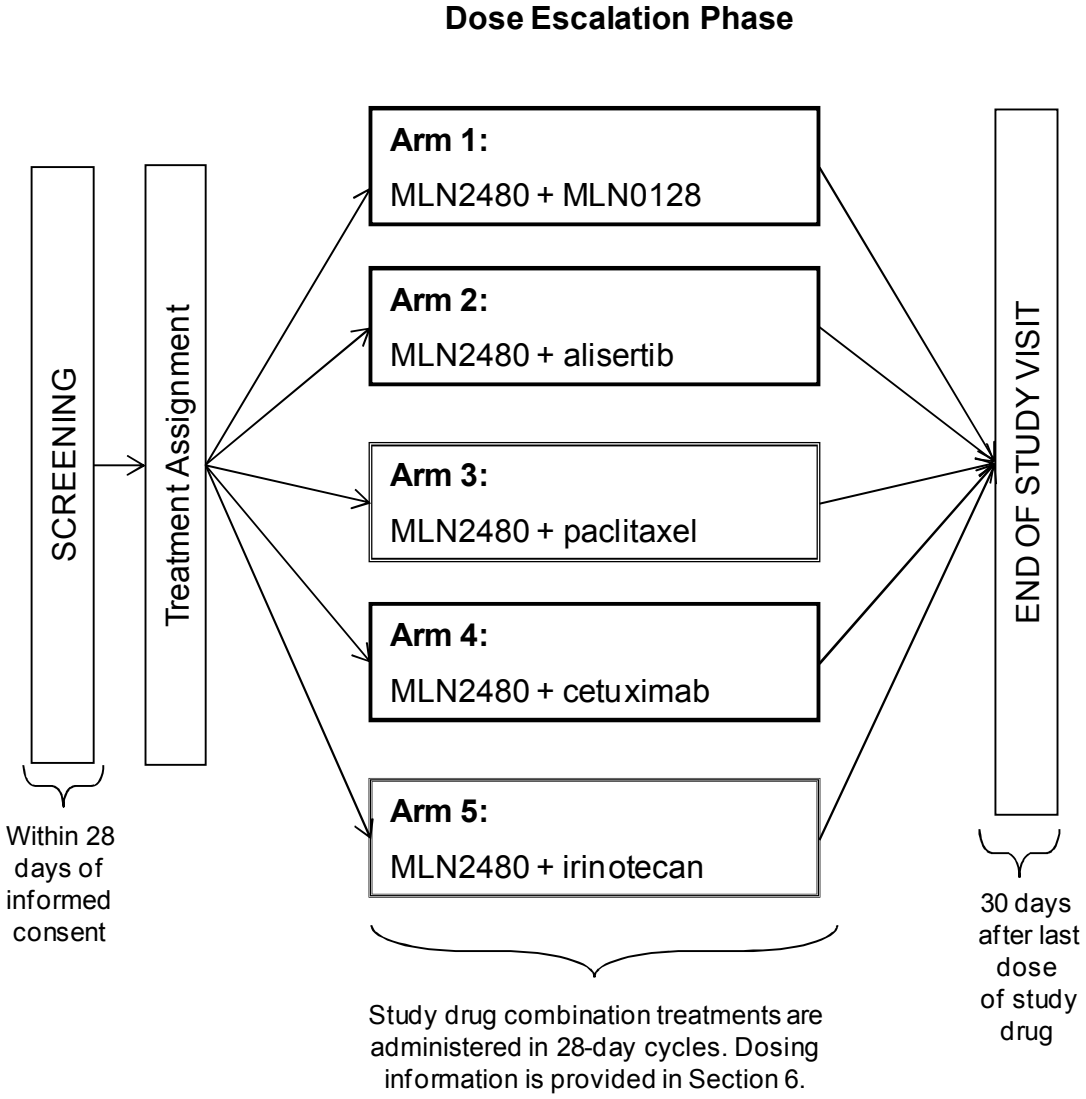
Underlying disease status will be assessed by the investigator per RECIST (version 1.1) guidelines using radiological evaluations (computed axial tomography [CT] scan or magnetic resonance imaging [MRI], CCI

Study Population: The study will enroll adult patients who have radiographically or clinically evaluable tumors and who, in the opinion of the treating physician, have failed standard therapies and for whom a phase 1 trial is an appropriate option. (***For Expansion phase***: Tumors must be measurable as defined by RECIST [version 1.1]) and of the protocol-specified genetic mutational status, where applicable). In addition to other requirements, all patients must have an Eastern Cooperative Oncology Group (ECOG) performance status 0-1, an expected survival of ≥ 3 months, a left ventricular ejection fraction (LVEF) of 50% or greater (as measured by echocardiogram [ECHO] or multiple gated acquisition [MUGA] scan), meet minimum clinical laboratory value requirements, be able to swallow and retain oral medications, and must agree to use effective birth control as appropriate. Patients who meet any of the following criteria are not eligible: history of uncontrolled brain metastasis, ongoing seizure disorder or a requirement for antiepileptic medications, recent (≤ 6 months) history of certain cardiac disorders, and gastrointestinal (GI) disease. Additional requirements and exclusions apply to specific combination treatment arms.

Duration of Study: Patient eligibility will be determined during screening (≤ 28 days before Cycle 1, Day 1). During the Treatment period, patients will take their assigned study drug combination in 28-day cycles until they experience disease progression, an unacceptable toxicity occurs, or discontinue for any other reason. Treatment in any patient will not exceed 12 cycles without sponsor approval. Patients who tolerate treatment and have evidence of clinical benefit after 12 cycles in the opinion of the investigator may continue treatment with continued monitoring upon prior review and approval by the project clinician.

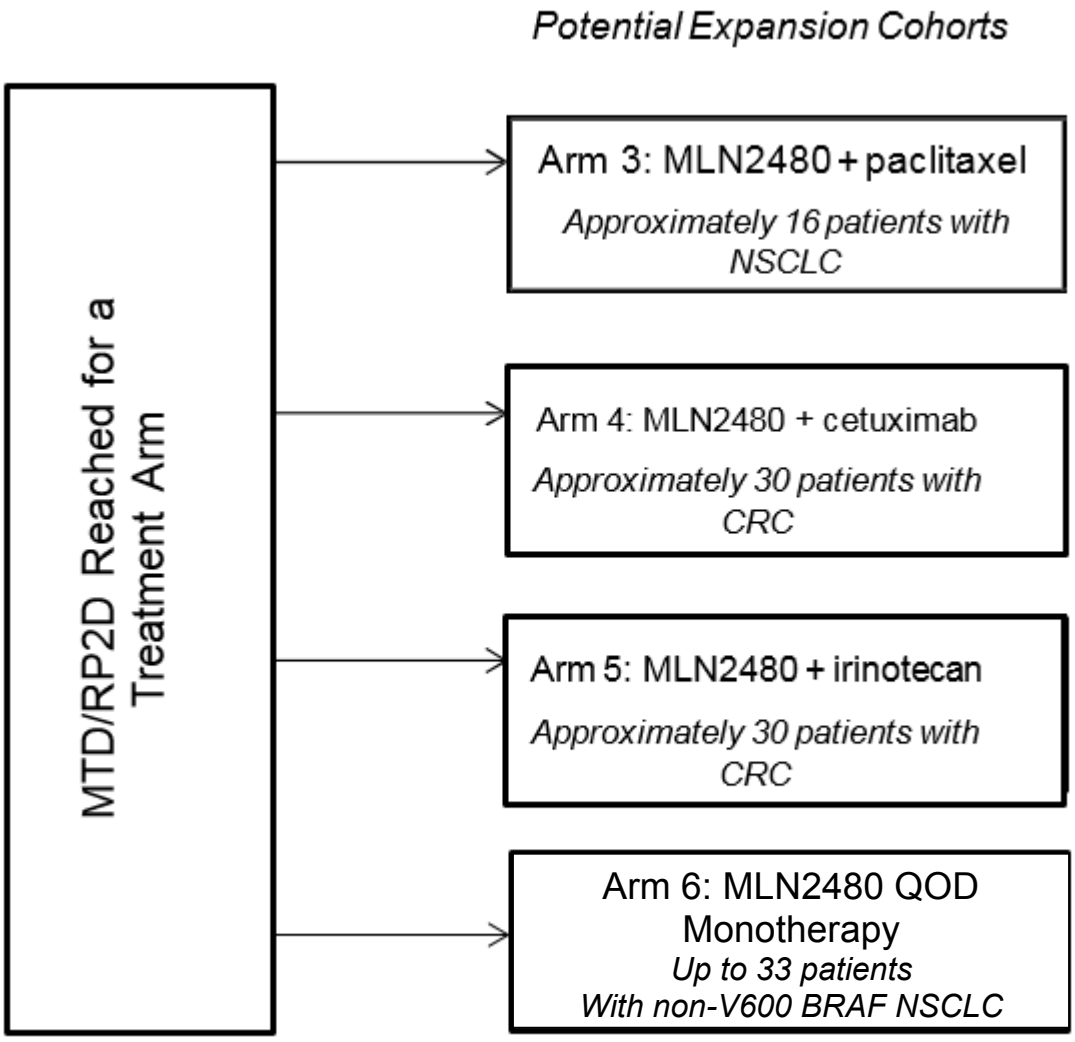
Each patient will attend an End of Study visit 30 days (+ 10 days) after his/her last study drug dose, or as of the start of subsequent anticancer therapy, whichever occurs first, to permit the detection of any delayed treatment-related AEs.

STUDY OVERVIEW DIAGRAM



Following review of preliminary data from the Escalation phase, the Expansion phase will investigate up to 3 treatment combinations.

DOSE EXPANSION PHASE



Schedules of Events for Arm 1 (MLN2480 + MLN0128)

Table 1.1 ARM 1 (MLN2480 + MLN0128): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)									End of Study (EOS)[a]
		1	2	3	10 (predose)	10 (postdose)	11	12	15	22	
Informed consent form	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history[b]	X										
Physical examination (including height[c] & weight)	X	X			X						X
Dermatological examination[d]	X	X[e]			X				X	X	X
Vital signs (temperature, blood pressure, heart rate)[f,g]	X	X	X	X[g]	X	X			X	X	X
ECHO or MUGA scan	X										
NYHA assessment	X										
12-lead safety ECG[f,h]	X	X		X	X						
Patient diary review	X	X		X	X				X	X	X
ECOG performance status	X	X [e]									X
Concomitant therapy & procedures recording	Concomitant therapy and procedures must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first										
SAE collection[i]	SAEs are recorded from the signing of Informed Consent through 30 days after the last study drug dose										
AE reporting[i]	AEs are recorded from the first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first										

Table 1.1 ARM 1 (MLN2480 + MLN0128): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)									End of Study (EOS)[a]
		1	2	3	10 (predose)	10 (postdose)	11	12	15	22	
SAMPLES AND LABORATORY ASSESSMENTS[e]											
Hematology[j] and serum chemistry	X	X [e,k]	X	X	X			X		X	X
HbA1c	X										
Fasting glucose[l]	X	Measured daily (predose) for Cycle 1.									X
Fasting lipid profile	X	X[e]	X	X	X						X
Thyroid function test[m]	X	X									
Urinary phosphate[n]	To be performed as clinically indicated										
Vitamin D	To be performed as clinically indicated										
Bone marrow aspirate & biopsy		Consider for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion									
Coagulation	X		See Section 7.4.16 and Section 7.4.19.1								
Pregnancy test[o]	X	X									X
Urinalysis (predose)	X	X[e]									X
CCI											
CCI											
Blood samples for PK assessment (see Table 1.2)[i]					X	X	X	X			
Archival or fresh tumor biopsy[q]	X										
DISEASE ASSESSMENT											
Disease evaluation, including CT or MRI scan[r]	X										X
STUDY DRUG DOSING											
MLN2480 dosing[s]	MLN2480 dosing: Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26										

Table 1.1 ARM 1 (MLN2480 + MLN0128): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)									End of Study (EOS)[a]
		1	2	3	10 (predose)	10 (postdose)	11	12	15	22	
MLN0128 dosing[s]	MLN0128 dosing: Days 2, 3, 4, 9, 10, 11, 16, 17, 18, 23, 24, and 25										

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI [redacted]; C*x*D*x* = Cycle *x*, Day *x*; DNA = deoxyribonucleic acid; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOS = end of study; HbA1c = glycosylated hemoglobin; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); NYHA = New York Heart Association; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

An End-of-Cohort safety data meeting scheduled by the sponsor will occur after the last patient in each cohort in the Dose Escalation phase has completed the first treatment cycle/DLT observation period (ie, Day 1 to Day 28) to facilitate careful assessment of AEs before escalating to the next dose.

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

a The End of Study visit will occur 30 (+ 10) days after the last dose of study treatment or the start of subsequent antineoplastic therapy, whichever occurs first.

b AEs that occur during the Screening period (following informed consent, but prior to study drug administration) will be recorded as part of the patient's medical history.

c Height is collected at screening only.

d All patients will be assessed by the investigator or a consulting dermatologist at the specified visits. The screening examination may include digital photographs. Existing lesions will be monitored throughout the study and documented in digital photographs. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/dermatologist. See Section 7.4.7.

e Unless otherwise specified, the assessment need not be repeated if the prior assessment was performed ≤ 72 hours before the scheduled visit.

f When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital sign and ECG procedures will be completed before the collection of the blood sample.

g Unless noted otherwise, vital signs will be measured ≤ 15 minutes predose. On Cycle 1, Day 10, vital signs will be measured 20 minutes after the dose, before the 0.5-hour PK sample. On Cycle 1, Day 3 only, vital signs will be measured after the dose at 2 hours (± 10 minutes).

h A single 12-lead ECG will be collected at screening in all patients to assess eligibility. All other ECGs will be conducted predose following the measurement of vital signs, unless otherwise indicated.

i In addition to the scheduled PK sample collections, a plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of the AE occurrence. See Section 7.4.18.

Table 1.1 ARM 1 (MLN2480 + MLN0128): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)									End of Study (EOS)[a]
		1	2	3	10 (predose)	10 (postdose)	11	12	15	22	
j If a patient develops an ANC < 500/µL or a platelet count < 25,000/µL, blood samples must be collected every 2 to 3 days, and study treatment withheld until counts resolve or until ANC returns to > 1000/µL and platelets return to > 50,000/µL.											
k Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1.											
l Fasting glucose will be measured at screening; predose daily during Cycles 1 and 2; at other times as clinically indicated; and at the EOS visit. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each measurement. In-home fasting glucose monitoring is required on days when fasting glucose is not measured in the clinic (Days 2, 4-9, 13, 14, 16-21, and 23-28). Patients will be given a glucometer on Cycle 1, Day 1 to monitor daily fasting glucose levels at home and will be instructed to notify the study clinician when fasting glucose is abnormal (ie, ≥ 150 mg/dL).											
m Thyroid function tests (TSH, T3, and T4) to be assessed at screening. In addition, TSH will be assessed on Cycle 1, Day 1.											
n Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).											
o For women of reproductive potential, only. Screening and EOS pregnancy tests must be serum. Either urine or serum pregnancy test is permitted at Cycle 1, Day 1.											
p Plasma sample will be taken ≤ 1 hour before MLN2480 dosing.											
q CCI [redacted]											
r 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. Disease assessments by RECIST (CT or MRI) will be performed every 2 cycles beginning Cycle 2, Day 27 (± 2 days), and at the EOS visit. Disease assessments need not be repeated at EOS visit if prior assessment was performed ≤ 4 weeks. See Section 7.4.20.											
s On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 and of MLN0128 at home. See Section 6.1.1 and Section 6.1.2 for fasting requirements and dosing and instructions for Arm 1.											

Table 1.2 Pharmacokinetic Sampling Schedule for ARM 1 (MLN2480 + MLN0128)—Escalation Phase

Sampling Time (Cycle 1, Day 10)	MLN2480	MLN0128
Predose	X	X
0.5 hour postdose (± 5 minutes)	X	X
1 hour postdose (± 5 minutes)	X	X
2 hours postdose (± 15 minutes)	X	X
4 hours postdose (± 15 minutes)	X	X
6 hours postdose (± 30 minutes)	X	X
8 hours postdose (± 45 minutes)	X	X
24 hours postdose (± 1 hour) (Day 11)	X[a]	X[a]
48 hours postdose (± 2 hours)[b] (Day 12)	X	

See Section 7.4.18 and the Laboratory Manual for specific instructions pertaining to pharmacokinetic (PK) sampling and processing.
PK samples may be drawn at the time of AEs leading to treatment interruption/reduction.
a The 24-hour postdose PK sample is collected before MLN2480 and MLN0128 dosing on Cycle 1, Day 11.
b The 48-hour postdose PK sample is collected before MLN2480 dosing on Cycle 1, Day 12.

Table 1.3 ARM 1 (MLN2480 + MLN0128): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
Physical examination & weight measurement	X			X
Dermatological examination[a]	X			X
Vital signs (temperature, blood pressure, heart rate)[b,c]	X	X		X
ECHO or MUGA scan			X[d]	
12-lead safety ECG (predose)[c]	X			
ECOG performance status	X			X
Patient diary review	X	X		X
Concomitant therapy & procedures recording	Concomitant therapy and procedures must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAE reporting[e]	SAEs will be collected from signing of Informed Consent through 30 days after the last dose of study drug			
AE reporting[e]	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAMPLES AND LABORATORY ASSESSMENTS[c,e]				
Hematology[f] & serum chemistry	X[g]	X		X
Thyroid function test (TSH)	X			
Fasting glucose[h]	Cycle 2: Measured daily(predose) Cycles ≥ 3: Day 1 (predose)			X
Glycosylated hemoglobin (HbA1c)	Every 3 cycles, beginning Cycle 3, Day 1			
Fasting lipid profile (predose)	Measured on Day 1 of Cycles ≥ 3, at the EOS visit, and as clinically indicated			X
Urinary phosphate[i]	To be performed as clinically indicated			
Vitamin D	To be performed as clinically indicated			
Bone marrow aspirate and biopsy	Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion			

Table 1.3 ARM 1 (MLN2480 + MLN0128): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
Coagulation	See Section 7.4.16 and Section 7.4.19.1			
Pregnancy test[j]				X
Urinalysis (predose)	X			X
CCI				
DISEASE ASSESSMENTS				
Response assessment, including CT or MRI scan[l]			X	X
STUDY DRUG DOSING				
MLN2480 dosing[m]	MLN2480 dosing: Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26			
MLN0128 dosing[m]	MLN0128 dosing: Days 2, 3, 4, 9, 10, 11, 16, 17, 18, 23, 24, and 25			

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI ; C*x*D*x* = Cycle *x*, Day *x*; DNA = deoxyribonucleic acid; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOS = end of study; HbA1c = glycosylated hemoglobin; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a Includes documentation of any suspicious lesions. The examination need not be repeated if performed ≤ 72 hours before the visit. See Section 7.4.7.

b Vital signs will be measured predose (within 15 minutes before dosing), except at the EOS visit where no study drug is administered.

c When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, vital sign and ECG measurements will be completed first.

d To be performed on Cycle 2 Day 27, Cycle 4 Day 27, and every 4 cycles thereafter on Day 27 (ie, Cycle 8 Day 27, Cycle 12 Day 27), or as clinically indicated.

e A plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged by the investigator to be treatment-related, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

f If a patient develops an ANC < 500/µL or platelet count < 25,000/µL, blood samples must be collected every 2 to 3 days and study treatment withheld until counts resolve or until ANC returns to > 1000/µL and platelets return to > 50,000/µL.

g Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle (see Section7.4.16.1). Hematology and serum chemistry for Day 1 of each cycle may be completed up to 72 hours before the visit.

h Fasting glucose will be measured daily (predose) in Cycle 2, predose on Day 1 of Cycles ≥ 3, at the EOS visit, and at other times as clinically indicated. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. Cycle 2: In-home fasting glucose monitoring is required on days when fasting glucose is not measured in the clinic. See Section 7.4.16.2.

i Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

Table 1.3 ARM 1 (MLN2480 + MLN0128): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	

j For women of reproductive potential, only. EOS pregnancy test must be serum.

k CCI [redacted]

l Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 2 cycles, beginning Cycle 2, Day 27 (± 2 days), and at the EOS visit. Assessments need not be repeated at the EOS visit if the prior assessment was performed ≤ 4 weeks. See Section 7.4.20.

m On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 and MLN0128 at home. See Section 6.1.1 and Section 6.1.2 for fasting requirements and dosing instructions.

Schedules of Events for Arm 2 (MLN2480 + Alisertib)

Table 1.4 ARM 2 (MLN2480 +Alisertib): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	10 (predose)	10 (postdose)	11	12	15	22	
Informed consent form	X								
Inclusion/exclusion criteria	X								
Demographics	X								
Medical history[b]	X								
Physical examination (including height[c] & weight)	X	X	X						X
Vital signs (temperature, blood pressure, heart rate)[d,e]	X	X[e]	X	X			X	X	X
Dermatological examination[f]	X	X[g]	X				X	X	X
ECHO or MUGA scan	X								
12-lead safety ECG[d,h]	X	X	X						
Patient diary review	X	X	X				X	X	X
ECOG performance status	X	X[g]							X
Concomitant therapy & procedures recording	Concomitant therapy and procedures must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first								
SAE collection[i]	SAEs are recorded from the signing of Informed Consent through 30 days after the last dose of study drug								
AE reporting[i]	AEs are recorded from the first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first								
SAMPLES AND LABORATORY ASSESSMENTS[d]									
Hematology[j] & serum chemistry	X	X[g,k]	X				X	X	X
Thyroid function tests[l]	X	X							

Table 1.4 ARM 2 (MLN2480 +Alisertib): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	10 (predose)	10 (postdose)	11	12	15	22	
Urinary phosphate[m]	To be performed as clinically indicated								
Vitamin D	To be performed as clinically indicated								
Bone marrow aspirate & biopsy		Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion.							
Coagulation	X	See Section 7.4.16 and Section 7.4.19.1							
Pregnancy test[n]	X	X							X
Urinalysis (predose)	X	X[g]							X
CCI									
CCI									
Blood samples for PK assessment (see Table 1.5)[i]			X	X	X	X			
Archival or fresh tumor biopsy[p]	X								
DISEASE ASSESSMENT									
Disease evaluation, including CT or MRI scan[q]	X								X
STUDY DRUG DOSING									
MLN2480 dosing[r]	MLN2480 dosing: Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26								
Alisertib dosing[r]	Alisertib dosing: (BID) Days 1, 2, 3, 8, 9, 10, 15, 16, and 17								

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; ctDNA = circulating tumor DNA; C*x*D*x* = Cycle *x*, Day *x*; DLT = dose-limiting toxicity; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOS = end of study; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

An End-of-Cohort safety data meeting scheduled by the sponsor will occur after the last patient in each cohort in the Dose Escalation phase has completed the first treatment cycle/DLT observation period (ie, Day 1 to Day 28) to facilitate careful assessment of AEs before escalating to the next dose.

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

Table 1.4 ARM 2 (MLN2480 +Alisertib): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	10 (predose)	10 (postdose)	11	12	15	22	

a The End of Study visit will occur 30 (+ 10) days after the last dose of study treatment or the start of subsequent antineoplastic therapy, whichever occurs first.

b AEs that occur during the Screening period (following informed consent, but prior to study drug administration) will be recorded as part of the patient's medical history.

c Height is collected at screening only.

d When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

e Unless noted otherwise, vital signs will be measured ≤ 15 minutes predose. On Cycle 1, Day 1 only, they will also be measured after the dose at 2 hours (± 10 minutes). On Cycle 1, Day 10, vital signs will be measured 20 minutes post dose, prior to the 0.5 hour PK sample

f All patients will be assessed by the investigator or a consulting dermatologist at the specified visits. The screening dermatological examination may include digital photographs. Existing lesions will be monitored throughout the study and changes to the lesions will be documented in digital photographs. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist. See Section 7.4.7.

g The assessment need not be repeated if performed ≤ 72 hours before the scheduled visit, unless otherwise specified.

h A single 12-lead ECG will be collected at screening in all patients to assess eligibility. All other ECGs will be conducted before the dose after vital signs are measured, unless otherwise indicated.

i In addition to the scheduled PK sample collections, a plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

j If a patient develops ANC < 500/μL or platelet count < 25,000/μL, blood samples must be collected every 2 to 3 days, and study treatment withheld until counts returns to > 1000/μL and platelets return to > 50,000/μL.

k Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle. See Section 7.4.16.1.

l Thyroid function tests (TSH, T3, and T4) to be assessed at screening. In addition, TSH will be assessed on Cycle 1, Day 1.

m Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

n For women of reproductive potential, only. Screening and EOS pregnancy tests must be serum. At Cycle 1, Day 1 only, the pregnancy test may be either urine or serum.

o CCI [redacted]

p An archival tumor tissue block or 10 slides from the diagnostic biopsy or surgical specimen from the most recent diagnosis will be requested for all patients at screening. If the archived sample is unavailable or inadequate (eg < 10 slides), a fresh biopsy may be required. The fresh biopsy specimens must be obtained at least 2 days after the last dose of any prior anticancer therapy and within 28 days before the first dose of study drug. See Section 7.4.19 and Section 7.4.19.1.

Table 1.4 ARM 2 (MLN2480 +Alisertib): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	10 (predose)	10 (postdose)	11	12	15	22	

q 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. Disease assessments by RECIST (CT or MRI) will be performed every 2 cycles beginning Cycle 2, Day 27 (± 2 days), and at the EOS visit. Assessments need not be repeated at the EOS visit if the prior assessment was performed ≤ 4 weeks. See Section 7.4.20.

r On dosing days when a clinic visit is not scheduled, patients will take their doses of MLN2480 and alisertib at home. See Section 6.1.1 and Section 6.1.3 for fasting requirements and dosing instructions.

Table 1.5 Pharmacokinetic Sampling Schedule for ARM 2 (MLN2480 + Alisertib)—Escalation Phase

Sampling Time (Cycle 1, Day 10)	MLN2480	Alisertib
Predose	X	X
0.5 hour postdose (± 5 minutes)	X	
1 hour postdose (± 5 minutes)	X	X
2 hours postdose (± 10 minutes)	X	X
3 hours postdose (± 15 minutes)	X	X
4 hours postdose (± 15 minutes)	X	X
6 hours postdose (± 30 minutes)	X	X
8 hours postdose (± 45 minutes)	X	X
12 hours postdose (± 2 hour)		X[a]
24 hours postdose (± 2 hour) (Day 11)	X	
48 hours postdose (± 2 hours)[b] (Day 12)	X	

See Section 7.4.18 and the Laboratory Manual for specific instructions pertaining to pharmacokinetic (PK) sampling and processing.

PK samples may be drawn at the time of AEs leading to treatment interruption/reduction.

a The 24-hour postdose PK sample is collected before the afternoon dosing of alisertib on Cycle 1, Day 10.

b The 48-hour PK sample is collected before MLN2480 dosing on Cycle 1, Day 12.

Table 1.6 ARM 2 (MLN2480 + Alisertib): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 & SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
Physical examination and weight measurement	X			X
Dermatological examination[a]	X			X
Vital signs (temperature, blood pressure, heart rate)[b, c]	X	X		X
ECHO or MUGA scan			X[d]	
12-lead safety ECG (predose)[b]	X			
ECOG performance status	X			X
Patient diary review	X	X		X
Concomitant therapy & procedures recording	Must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAE reporting[e]	SAEs will be collected from the signing of Informed Consent through 30 days after the last dose of study drug			
AE reporting[e]	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAMPLES AND LABORATORY ASSESSMENTS[b,e]				
Hematology[f] and serum chemistry	X[g]	X		X
Thyroid function test (TSH)	X			
Urinary phosphate[h]	To be performed as clinically indicated			
Vitamin D	To be performed as clinically indicated			
Bone marrow aspirate and biopsy	Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion			
Coagulation	See Section 7.4.16 and Section 7.4.19.1			
Pregnancy test[i]				X
Urinalysis (predose)	X			X
CCI [redacted]				

Table 1.6 ARM 2 (MLN2480 + Alisertib): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 & SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
DISEASE ASSESSMENT				
Disease evaluation, including CT or MRI scan[k]			X	X
STUDY DRUG DOSING				
MLN2480 dosing[l]	MLN2480 dosing: Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26			
Alisertib dosing[l]	Alisertib dosing: (BID) Days 1, 2, 3, 8, 9, 10, 15, 16, and 17			

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI ; C*x*D*x* = Cycle *x*, Day *x*; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a Includes documentation of any suspicious lesions. Need not be repeated if the prior assessment was performed within 72 hours. See Section 7.4.7.

b When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

c Predose (within 15 minutes before dosing), except at the EOS visit where no study drug is administered.

d To be performed on Cycle 2 Day 27, Cycle 4 Day 27, and every 4 cycles thereafter on Day 27 (ie, Cycle 8 Day 27, Cycle 12 Day 27), or as clinically indicated.

e A plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged by the investigator to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

f If a patient develops ANC < 500/µL or a platelet count < 25,000/µL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/µL and platelets return to > 50,000/µL.

g Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1. Hematology and serum chemistry samples for the Day 1 assessments for each cycle may be obtained up to 72 hours before the scheduled visit.

h Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

i For women of reproductive potential, only. EOS pregnancy test must be serum.

j CCI

k Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 8 weeks beginning Cycle 2, Day 27 (± 2 days) and at the EOS visit. The assessment at the EOS visit need not be repeated if performed within 4 weeks before the visit. See Section 7.4.20.

l On dosing days when the patient does not have a clinic visit, patients will take their doses of MLN2480 and alisertib at home. See Section 6.1.1 and Section 6.1.3 for fasting requirements and additional dosing instructions.

Schedules of Events for Arm 3 (MLN2480 + Paclitaxel)

Table 1.7 ARM 3 (MLN2480 + Paclitaxel): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	8	15 (predose)	15 (postdose)	16	17	22	
Informed consent form	X								
Inclusion/exclusion criteria	X								
Demographics	X								
Medical history[b]	X								
Physical examination (including height[c] & weight)	X	X	X	X					X
Dermatological examination[d]	X	X[e]	X	X				X	X
Vital signs (temperature, blood pressure, heart rate)[f,g]	X	X[g]	X	X	X				X
ECHO or MUGA scan	X								
12-lead safety ECG[f,h]	X	X		X					X
Patient diary review	X	X	X	X				X	X
ECOG performance status	X	X[e]							X
Concomitant therapy & procedures recording	Concomitant therapy and procedures must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first								
SAE collection[i]	SAEs will be collected from the signing of Informed Consent through 30 days after the last dose of study drug								
AE reporting[i]	AEs will be recorded from the first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first								
SAMPLES AND LABORATORY ASSESSMENTS[e,h]									
Hematology[j] & serum chemistry	X	X [e,k]	X	X				X	X
Thyroid function tests[l]	X	X							

Table 1.7 ARM 3 (MLN2480 + Paclitaxel): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	8	15 (predose)	15 (postdose)	16	17	22	
Urinary phosphate[m]	To be performed as clinically indicated								
Vitamin D	To be performed as clinically indicated								
Bone marrow aspirate & biopsy		Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion							
Coagulation	X	See Section 7.4.16 and Section 7.4.19.1							
Pregnancy test[n]	X	X							X
Urinalysis (predose)	X	X[e]							X
CCI									
CCI									
Blood samples for pharmacokinetic assessment (see Table 1.8)[i,p]				X[o]	X[o]	X[o]	X[o]		
Archival or fresh tumor biopsy[q]	X								
DISEASE ASSESSMENT									
Disease evaluation, including CT or MRI scan[r]	X								**X**
STUDY DRUG DOSING									
MLN2480 dosing[s]		MLN2480 dosing: Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26							
MLN2480 dosing[s]		MLN2480 QW dosing: Days 2, 9, 16, and 23							
Paclitaxel dosing[s]		Paclitaxel infusion: Days 1, 8, and 15							

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI ; C*x*D*x* = Cycle *x*, Day *x*; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = case report form; EOS = end of study; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic(s); QOD = every other day; QW = once weekly; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Table 1.7 ARM 3 (MLN2480 + Paclitaxel): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	8	15 (predose)	15 (postdose)	16	17	22	

An End-of-Cohort safety data meeting scheduled by the sponsor will occur after the last patient in each cohort in the Dose Escalation phase has completed the first treatment cycle/DLT observation period (ie, Day 1 to Day 28) to facilitate careful assessment of AEs before escalating to the next dose.

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

a The End of Study visit will occur 30 (+ 10) days after the last dose of study treatment or the start of subsequent antineoplastic therapy, whichever occurs first.

b AEs that occur during the Screening period (following informed consent, but prior to study drug administration) will be recorded as part of the patient's medical history

c Height is to be collected at screening only.

d All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. The screening examination may include digital photographs. Existing lesions will be monitored throughout the study, and changes to the lesions will be documented in digital photographs. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/dermatologist. See Section 7.4.7.

e Assessments need not be repeated if performed within 72 hours before the visit, unless otherwise specified.

f When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

g Unless noted otherwise, vital signs will be measured ≤ 15 minutes predose. On Cycle 1, Day 1 only, vital signs are also measured after the dose at 2 hours (± 10 min). On Cycle 1, Day 15, vital signs will be measured 20 minutes after the start of the infusion.

h A single 12-lead ECG will be collected at screening in all patients to assess eligibility. All other ECGs will be conducted before the dose, after vital signs are measured, unless otherwise indicated.

i In addition to the scheduled PK sample collections, a plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

j If a patient develops ANC < 500/μL or a platelet count < 25,000/μL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/μL and platelets return to > 50,000/μL.

k Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1.

l Thyroid function tests (TSH, T3, and T4) to be assessed at screening. In addition, TSH only will be assessed on Cycle 1, Day 1.

m Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

Table 1.7 ARM 3 (MLN2480 + Paclitaxel): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)							End of Study (EOS)[a]
		1	8	15 (predose)	15 (postdose)	16	17	22	

n For women of reproductive potential, only. Screening and EOS pregnancy tests must be serum. Either a urine or serum pregnancy test is permitted at Cycle 1, Day 1, only.

o CCI [redacted] the work week to avoid overlapping clinic visits on weekends or holidays.

q An archival tumor tissue block or 10 slides from the diagnostic biopsy or surgical specimen from the most recent diagnosis will be requested for all patients at screening. If the archived sample is unavailable or inadequate (eg < 10 slides), a fresh biopsy may be required. The fresh biopsy specimens must be obtained at least 2 days after the last dose of any prior anticancer therapy and within 28 days before the first dose of study drug. See Section 7.4.19 and Section 7.4.19.1.

r 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. Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 8 weeks (± 2 days) beginning on Cycle 2, Day 27 (± 2 days) and at the EOS visit. Assessments need not be repeated if performed within 4 weeks before the End of Study visit. See Section 7.4.20.

s Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when a clinic visit is not scheduled, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.4 for dosing instructions for Arm 3.

Table 1.8 Pharmacokinetic Sampling for ARM 3 (MLN2480 QOD Dosing + Paclitaxel)—Escalation Phase and (if applicable) Expansion Phase

Sampling Time (Cycle 1, Day 15)	MLN2480	Sampling Time (Cycle 1: Days 15, 16, and 17)	Paclitaxel
Predose[a]	X	Predose[a]	X
MLN2480 Dose Administration		Paclitaxel 1-hr infusion	
0.5 hour postdose (± 5 minutes)	X	End of infusion (± 5 minutes)[b]	X
1 hour postdose (± 5 minutes)	X	5 min post-EOI (± 2 minutes)	X
2 hours postdose (± 10 minutes)	X	15 min post-EOI (± 2 minutes)	X
4 hours postdose (± 15 minutes)	X	30 min post-EOI (± 5 minutes)	X
6 hours postdose (± 30 minutes)	X	1 hour post-EOI (± 5 minutes)	X
8 hours postdose (± 45 minutes)	X	2 hours post-EOI (± 10 minutes)	X
24 hours postdose (± 1 hour) (Day 16)	X	3 hours post-EOI (± 15 minutes)	X
48 hours postdose (± 2 hours)[c] (Day 17)	X	7 hours post-EOI (± 30 minutes)	X
		10 hours post-EOI (± 2 hours)	X
		23 hours post-EOI (± 2 hours) (Day 16)	X
		47 hours post-EOI (± 2 hours) (Day 17)	X

Abbreviations: EOI = End of Infusion QOD = every other day.

See Section 7.4.18 and the Laboratory Manual for specific instructions pertaining to pharmacokinetic (PK) sampling and processing.

PK samples may be drawn at the time of AEs leading to treatment interruption/reduction.

a MLN2480 should be administered 1 hour before the start of the paclitaxel infusion.

b End of infusion PK sample is collected immediately before shut off of infusion pump (± 5 minutes).

c The 48-hour PK sample is collected before MLN2480 dosing on Cycle 1, Day 17.

Table 1.9 Pharmacokinetic Sampling for ARM 3 (MLN2480 QW Dosing + Paclitaxel)—Escalation Phase and (if applicable) Expansion Phase

Sampling Time (Cycle 1, Day 16)	MLN2480	Sampling Time (Cycle 1: Days 15, 16, and 17)	Paclitaxel
Predose [a]	X	Predose [a]	X
MLN2480 Dose Administration		Paclitaxel 1-hr infusion	
0.5 hour postdose (± 5 minutes)	X	End of infusion (± 5 minutes)[b]	X
1 hour postdose (± 5 minutes)	X	5 min post-EOI (± 2 minutes)	X
2 hours postdose (± 10 minutes)	X	15 min post-EOI (± 2 minutes)	X
4 hours postdose (± 15 minutes)	X	30 min post-EOI (± 5 minutes)	X
6 hours postdose (± 30 minutes)	X	1 hour post-EOI (± 5 minutes)	X
8 hours postdose (± 45 minutes)	X	2 hours post-EOI (± 10 minutes)	X
24 hours postdose (± 3 hour) (Day 17)	X	3 hours post-EOI (± 15 minutes)	X
144 hours postdose (± 6 hours) (Day 22)	X	6 hours post-EOI (± 30 minutes)	X
		10 hours post-EOI (± 2 hours)	X
		23 hours post-EOI (± 2 hours)[d] (Day 16)	X
		47 hours post-EOI (± 3 hours) (Day 17)	X

Abbreviations: EOI = End of Infusion.

See Section 7.4.18 and the Laboratory Manual for specific instructions pertaining to pharmacokinetic (PK) sampling and processing.

PK samples may be drawn at the time of AE's leading to treatment interruption/reduction.

a Note with MLN2480 QW schedule, PK sampling for paclitaxel dosing begins on Cycle 1 Day 15 and PK sampling for MLN2480 dosing begins on Cycle 1 Day 16.

b End of infusion PK sample is collected immediately before shut off of infusion pump (± 5 minutes).

c The 23-hour paclitaxel PK sample is collected before MLN2480 dosing on Cycle 1, Day 16.

Table 1.10 ARM 3 (MLN2480 + Paclitaxel): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
Physical examination & weight measurement	X			X
Dermatological examination[a]	X			X
Vital signs (temperature, blood pressure, heart rate)[b,c]	X	X		X
ECHO or MUGA scan			X[d]	
12-lead safety ECG(predose)[c]	X			X
ECOG performance status	X			X
Patient diary review	X	X		X
Concomitant therapy and procedures recording	Must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAE reporting[e]	SAEs will be collected from signing of Informed Consent through 30 days after the last dose of study drug			
AE reporting[e]	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAMPLES AND LABORATORY ASSESSMENTS[c]				
Hematology[f] & serum chemistry	X[g]	X		X
Thyroid function test (TSH)	X			
Urinary phosphate[h]	To be performed as clinically indicated			
Vitamin D	To be performed as clinically indicated			
Bone marrow aspirate and biopsy	Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion.			
Coagulation	See Section 7.4.16 and Section 7.4.19.1			
Pregnancy test[i]				X
Urinalysis (predose)	X			X
CCI [redacted]				

Table 1.10 ARM 3 (MLN2480 + Paclitaxel): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
DISEASE ASSESSMENT				
Disease evaluation, including CT or MRI scan[k]			X	X
STUDY DRUG DOSING				
MLN2480 dosing[l]	MLN2480 dosing: Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26			
MLN2480 dosing[l]	MLN2480 QW dosing: Days 2, 9, 16 and 23			
Paclitaxel dosing[l]	Paclitaxel infusion: Days 1, 8, and 15			

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI [redacted]; C*x*D*x* = Cycle *x*, Day *x*; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a Includes documentation of any suspicious lesions. Need not be repeated if the prior assessment was performed within 72 hours. See Section 7.4.7.

b Predose (within 15 minutes before dosing).

c When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

d To be performed on Cycle 2 Day 27, Cycle 4 Day 27, and every 4 cycles thereafter on Day 27 (ie, Cycle 8 Day 27, Cycle 12 Day 27), or as clinically indicated.

e A plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

f If a patient develops ANC < 500/µL or platelet count < 25,000/µL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/µL and platelets return to > 50,000/µL.

g Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1. Samples for the Day 1 assessments for each cycle may be obtained up to 72 hours before the study visit.

h Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

i

j CCI [redacted]

k Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 2 cycles beginning Cycle 2, Day 27 (± 2 days), and at the EOS visit. Disease assessments need not be repeated if performed within 4 weeks prior to the End of Study visit. See Section 7.4.20.

l Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.4 for additional dosing instructions for Arm 3.

Schedules of Events for Arm 4 (MLN2480 + Cetuximab)

Table 1.11 ARM 4 (MLN2480 + Cetuximab): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	8	15	16	17	22	
Informed consent form	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical history[b]	X							
Physical examination (including height[c] & weight)	X	X	X	X				X
Dermatological examination[d]	X	X[e]	X	X			X	X
Vital signs (temperature, blood pressure, heart rate)[f,g]	X	X[g]	X	X				X
ECHO or MUGA scan	X							
12-lead safety ECG[f,h]	X	X		X				X
Patient diary review	X	X	X	X			X	X
ECOG performance status	X	X[e]						X
Concomitant therapy & procedures recording	Concomitant therapy and procedures must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first							
SAE collection[i]	SAEs will be collected from the signing of Informed Consent through 30 days after the last dose of study drug							
AE reporting[i]	AEs will be recorded from the first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first							
SAMPLES AND LABORATORY ASSESSMENTS[e,h]								
Hematology[j] & serum chemistry	X	X [e,k]	X	X			X	X
Thyroid function tests[l]	X	X						

Table 1.11 ARM 4 (MLN2480 + Cetuximab): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	8	15	16	17	22	
Urinary phosphate[m]	To be performed as clinically indicated							
Vitamin D	To be performed as clinically indicated							
Bone marrow aspirate & biopsy		Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion						
Coagulation	X	See Section 7.4.16 and Section 7.4.19.1						
Pregnancy test[n]	X	X						X
Urinalysis (predose)	X	X[e]						X
CCI								
CCI								
Blood samples for pharmacokinetic assessment (see Table 1.12)[i,p]				X[p]	X[p]	X[p]	X	
Archival or fresh tumor biopsy[q]	X							
DISEASE ASSESSMENT								
Disease evaluation, including CT or MRI scan[r]	X							**X**
STUDY DRUG DOSING								
MLN2480 dosing[s]		MLN2480 dosing: Days 2, 9, 16, and 23						
Cetuximab dosing[s]		Cetuximab infusion: Days 1, 8, 15, and 22						

Table 1.11 ARM 4 (MLN2480 + Cetuximab): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	8	15	16	17	22	

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI ; C*x*D*x* = Cycle *x*, Day *x*; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = case report form; EOS = end of study; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

An End-of-Cohort safety data meeting scheduled by the sponsor will occur after the last patient in each cohort in the Dose Escalation phase has completed the first treatment cycle/DLT observation period (ie, Day 1 to Day 28) to facilitate careful assessment of AEs before escalating to the next dose.

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

a The End of Study visit will occur 30 (+ 10) days after the last dose of study treatment or the start of subsequent antineoplastic therapy, whichever occurs first.

b AEs that occur during the Screening period (following informed consent, but prior to study drug administration) will be recorded as part of the patient's medical history

c Height is to be collected at screening only.

d All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. The screening examination may include digital photographs. Existing lesions will be monitored throughout the study, and changes to the lesions will be documented in digital photographs. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/dermatologist. See Section 7.4.7.

e Assessments need not be repeated if performed within 72 hours before the visit, unless otherwise specified.

f When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

g Unless noted otherwise, vital signs will be measured ≤ 15 minutes predose. On Cycle 1 Day 1 only, vital signs are also measured after the dose at 2 hours (± 10 min). On Cycle 1 Day 15, vital signs will be measured 20 minutes after the start of the infusion.

h A single 12-lead ECG will be collected at screening in all patients to assess eligibility. All other ECGs will be conducted before the dose, after vital signs are measured, unless otherwise indicated.

i In addition to the scheduled PK sample collections, a plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

j If a patient develops ANC < 500/μL or a platelet count < 25,000/μL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/μL and platelets return to > 50,000/μL.

Table 1.11 ARM 4 (MLN2480 + Cetuximab): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	8	15	16	17	22	

k Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1.

l Thyroid function tests (TSH, T3, and T4) to be assessed at screening. In addition, TSH only will be assessed on Cycle 1 Day 1.

m Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

n For women of reproductive potential, only. Screening and EOS pregnancy tests must be serum. Either a urine or serum pregnancy test is permitted at Cycle 1 Day 1, only.

o CCI [redacted]

p Multiple daily PK sampling is required during Cycle 1 Days 15-17. It is recommended to initiate Cycle 1 Day 1 at the beginning of the work week to avoid overlapping clinic visits on weekends or holidays.

q An archival tumor tissue block or 10 slides from the diagnostic biopsy or surgical specimen from the most recent diagnosis will be requested for all patients at screening. If the archived sample is unavailable or inadequate (eg < 10 slides), a fresh biopsy may be required. The fresh biopsy specimens must be obtained at least 2 days after the last dose of any prior anticancer therapy and within 28 days before the first dose of study drug. See Section 7.4.19 and Section 7.4.19.1.

r 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. Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 8 weeks (± 2 days) beginning on Cycle 2, Day 27 (± 2 days) and at the EOS visit. Assessments need not be repeated if performed within 4 weeks before the End of Study visit. See Section 7.4.20.

s Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when a clinic visit is not scheduled, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.5 for dosing instructions for Arm 4.

Table 1.12 Pharmacokinetic Sampling for ARM 4 (MLN2480 QW Dosing + Cetuximab)—Escalation Phase and (if applicable) Expansion Phase

Sampling Time (Cycle 1, Day 16)	MLN2480	Sampling Time (Cycle 1: Days 15, 16, and 17)	Cetuximab
Predose [a]	X	Predose [a]	X
MLN2480 Dose Administration		Cetuximab 1-hr infusion (2-hrs for initial infusion)	
0.5 hour postdose (± 5 minutes)	X	End of infusion (± 5 minutes)[b]	X
1 hour postdose (± 5 minutes)	X	5 min post-EOI (± 2 minutes)	X
2 hours postdose (± 10 minutes)	X	15 min post-EOI (± 2 minutes)	X
4 hours postdose (± 15 minutes)	X	30 min post-EOI (± 5 minutes)	X
6 hours postdose (± 30 minutes)	X	1 hour post-EOI (± 5 minutes)	X
8 hours postdose (± 45 minutes)	X	2 hours post-EOI (± 10 minutes)	X
24 hours postdose (± 3 hour) (Day 17)	X	3 hours post-EOI (± 15 minutes)	X
144 hours postdose (± 6 hours) (Day 22)	X	6 hours post-EOI (± 30 minutes)	X
		10 hours post-EOI (± 2 hours)	X
		23 hours post-EOI (± 2 hours)[c] (Day 16)	X
		47 hours post-EOI (± 3 hours) (Day 17)	X
		168 hours postdose (± 6 hours) (Day 22) (within 1 hour prior to dose on Day 22)	X

Abbreviations: EOI = End of Infusion.

See Section 7.4.18 and the Laboratory Manual for specific instructions pertaining to pharmacokinetic (PK) sampling and processing.

a Note with MLN2480 QW schedule, PK sampling for Cetuximab dosing begins on Cycle 1 Day 15 and PK sampling for MLN2480 dosing begins on Cycle 1 Day 16.

b End of infusion PK sample is collected immediately before shut off of infusion pump (± 5 minutes).

c The 23-hour Cetuximab PK sample is collected before MLN2480 dosing on Cycle 1, Day 16.

Table 1.13 ARM 4 (MLN2480 + Cetuximab): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
Physical examination & weight measurement	X			X
Dermatological examination[a]	X			X
Vital signs (temperature, blood pressure, heart rate)[b,c]	X	X		X
ECHO or MUGA scan			X[d]	
12-lead safety ECG(predose)[c]	X			X
ECOG performance status	X			X
Patient diary review	X	X		X
Concomitant therapy and procedures recording	Must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAE reporting[e]	SAEs will be collected from signing of Informed Consent through 30 days after the last dose of study drug			
AE reporting[e]	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAMPLES AND LABORATORY ASSESSMENTS[c]				
Hematology[f] & serum chemistry	X[g]	X		X
Thyroid function test (TSH)	X			
Urinary phosphate[h]	To be performed as clinically indicated			
Vitamin D	To be performed as clinically indicated			
Bone marrow aspirate and biopsy	Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion.			
Coagulation	See Section 7.4.16 and Section 7.4.19.1.			
Pregnancy test[i]				X
Urinalysis (predose)	X			X
CCI				

Table 1.13 ARM 4 (MLN2480 + Cetuximab): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
DISEASE ASSESSMENT				
Disease evaluation, including CT or MRI scan[k]			X	X
STUDY DRUG DOSING				
MLN2480 dosing[l]	MLN2480 dosing: Days 2, 9, 16 and 23			
Cetuximab dosing[l]	Cetuximab infusion: Days 1, 8, 15, and 22			

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI [redacted]; C*x*D*x* = Cycle *x*, Day *x*; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a Includes documentation of any suspicious lesions. Need not be repeated if the prior assessment was performed within 72 hours. See Section 7.4.7.

b Predose (within 15 minutes before dosing).

c When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

d To be performed on Cycle 2 Day 27, Cycle 4 Day 27, and every 4 cycles thereafter on Day 27 (ie, Cycle 8 Day 27, Cycle 12 Day 27), or as clinically indicated.

e A plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

f If a patient develops ANC < 500/µL or platelet count < 25,000/µL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/µL and platelets return to > 50,000/µL.

g Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1. Samples for the Day 1 assessments for each cycle may be obtained up to 72 hours before the study visit.

h Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

i For women of reproductive potential, only. EOS pregnancy test must be serum.

j CCI [redacted]

k Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 2 cycles beginning Cycle 2 Day 27 (± 2 days), and at the EOS visit. Disease assessments need not be repeated if performed within 4 weeks prior to the End of Study visit. See Section 7.4.20.

l Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.5 for additional dosing instructions for Arm 4.

Schedules of Events for Arm 5 (MLN2480 + Irinotecan)

Table 1.14 ARM 5 (MLN2480 + Irinotecan): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	9	15	16	17	22	
Informed consent form	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical history[b]	X							
Physical examination (including height[c] & weight)	X	X	X	X				X
Dermatological examination[d]	X	X[e]	X	X			X	X
Vital signs (temperature, blood pressure, heart rate)[f,g]	X	X[g]	X	X				X
ECHO or MUGA scan	X							
12-lead safety ECG[f,h]	X	X		X				X
Patient diary review	X	X	X	X			X	X
ECOG performance status	X	X[e]						X
Concomitant therapy & procedures recording	Concomitant therapy and procedures must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first							
SAE collection[i]	SAEs will be collected from the signing of Informed Consent through 30 days after the last dose of study drug							
AE reporting[i]	AEs will be recorded from the first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first							
SAMPLES AND LABORATORY ASSESSMENTS[e,h]								
Hematology[j] & serum chemistry	X	X [e,k]	X	X			X	X
Thyroid function tests[l]	X	X						

Table 1.14 ARM 5 (MLN2480 + Irinotecan): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	9	15	16	17	22	
Urinary phosphate[m]	To be performed as clinically indicated							
Vitamin D	To be performed as clinically indicated							
Bone marrow aspirate & biopsy		Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion						
Coagulation	X	See Section 7.4.16 and Section 7.4.19.1						
Pregnancy test[n]	X	X						X
Urinalysis (predose)	X	X[e]						X
CCI [redacted] CCI								
Blood samples for pharmacokinetic assessment (see Table 1.15)[i,p]				X[p]	X[p]	X[p]	X	
Archival or fresh tumor biopsy[q]	X							
DISEASE ASSESSMENT								
Disease evaluation, including CT or MRI scan[r]	X							**X**
STUDY DRUG DOSING								
MLN2480 dosing[s]		MLN2480 dosing: Days 2, 9, 16, and 23						
Irinotecan dosing[s]		Irinotecan infusion: Days 1 and 15						

Table 1.14 ARM 5 (MLN2480 + Irinotecan): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	9	15	16	17	22	

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI ; C*x*D*x* = Cycle *x*, Day *x*; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = case report form; EOS = end of study; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

An End-of-Cohort safety data meeting scheduled by the sponsor will occur after the last patient in each cohort in the Dose Escalation phase has completed the first treatment cycle/DLT observation period (ie, Day 1 to Day 28) to facilitate careful assessment of AEs before escalating to the next dose.

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

a The End of Study visit will occur 30 (+ 10) days after the last dose of study treatment or the start of subsequent antineoplastic therapy, whichever occurs first.

b AEs that occur during the Screening period (following informed consent, but prior to study drug administration) will be recorded as part of the patient's medical history

c Height is to be collected at screening only.

d All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. The screening examination may include digital photographs. Existing lesions will be monitored throughout the study, and changes to the lesions will be documented in digital photographs. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/dermatologist. See Section 7.4.7.

e Assessments need not be repeated if performed within 72 hours before the visit, unless otherwise specified.

f When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

g Unless noted otherwise, vital signs will be measured ≤ 15 minutes predose. On Cycle 1 Day 1 only, vital signs are also measured after the dose at 2 hours (± 10 min). On Cycle 1 Day 15, vital signs will be measured 20 minutes after the start of the infusion.

h A single 12-lead ECG will be collected at screening in all patients to assess eligibility. All other ECGs will be conducted before the dose, after vital signs are measured, unless otherwise indicated.

i In addition to the scheduled PK sample collections, a plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

j If a patient develops ANC < 500/μL or a platelet count < 25,000/μL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/μL and platelets return to > 50,000/μL.

Table 1.14 ARM 5 (MLN2480 + Irinotecan): Cycle 1 Schedule of Events

PROCEDURES	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)						End of Study (EOS)[a]
		1	9	15	16	17	22	

k Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1.

l Thyroid function tests (TSH, T3, and T4) to be assessed at screening. In addition, TSH only will be assessed on Cycle 1 Day 1.

m Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

n For women of reproductive potential, only. Screening and EOS pregnancy tests must be serum. Either a urine or serum pregnancy test is permitted at Cycle 1 Day 1, only.

o CCI [redacted]

p Multiple daily PK sampling is required during Cycle 1 Days 15-17. It is recommended to initiate Cycle 1 Day 1 at the beginning of the work week to avoid overlapping clinic visits on weekends or holidays.

q An archival tumor tissue block or 10 slides from the diagnostic biopsy or surgical specimen from the most recent diagnosis will be requested for all patients at screening. If the archived sample is unavailable or inadequate (eg < 10 slides), a fresh biopsy may be required. The fresh biopsy specimens must be obtained at least 2 days after the last dose of any prior anticancer therapy and within 28 days before the first dose of study drug. See Section 7.4.19 and Section 7.4.19.1.

r 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. Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 8 weeks (± 2 days) beginning on Cycle 2, Day 27 (± 2 days) and at the EOS visit. Assessments need not be repeated if performed within 4 weeks before the End of Study visit. See Section 7.4.20.

s Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when a clinic visit is not scheduled, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.6 for dosing instructions for Arm 5.

Table 1.15 Pharmacokinetic Sampling for ARM 5 (MLN2480 QW Dosing + Irinotecan)—Escalation Phase and (if applicable) Expansion Phase

Sampling Time (Cycle 1, Day 16)	MLN2480	Sampling Time (Cycle 1: Days 15, 16, and 17)	Irinotecan (and SN-38 Metabolite)
Predose [a]	X	Predose [a]	X
MLN2480 Dose Administration		Irinotecan 30-90 minute infusion	
0.5 hour postdose (± 5 minutes)	X	End of infusion (± 5 minutes)[b]	X
1 hour postdose (± 5 minutes)	X	5 min post-EOI (± 2 minutes)	X
2 hours postdose (± 10 minutes)	X	15 min post-EOI (± 2 minutes)	X
4 hours postdose (± 15 minutes)	X	30 min post-EOI (± 5 minutes)	X
6 hours postdose (± 30 minutes)	X	1 hour post-EOI (± 5 minutes)	X
8 hours postdose (± 45 minutes)	X	2 hours post-EOI (± 10 minutes)	X
24 hours postdose (± 3 hour) (Day 17)	X	3 hours post-EOI (± 15 minutes)	X
144 hours postdose (± 6 hours) (Day 22)	X	6 hours post-EOI (± 30 minutes)	X
		10 hours post-EOI (± 2 hours)	X
		23 hours post-EOI (± 2 hours)[d] (Day 16)	X
		47 hours post-EOI (± 3 hours) (Day 17)	X

Abbreviations: EOI = End of Infusion.

See Section 7.4.18 and the Laboratory Manual for specific instructions pertaining to pharmacokinetic (PK) sampling and processing.

a Note with MLN2480 QW schedule, PK sampling for Irinotecan dosing begins on Cycle 1 Day 15 and PK sampling for MLN2480 dosing begins on Cycle 1 Day 16.

b End of infusion PK sample is collected immediately before shut off of infusion pump (± 5 minutes).

c The 23-hour irinotecan PK sample is collected before MLN2480 dosing on Cycle 1 Day 16.

Table 1.16 ARM 5 (MLN2480 + Irinotecan): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
Physical examination & weight measurement	X			X
Dermatological examination[a]	X			X
Vital signs (temperature, blood pressure, heart rate)[b,c]	X	X		X
ECHO or MUGA scan			X[d]	
12-lead safety ECG(predose)[c]	X			X
ECOG performance status	X			X
Patient diary review	X	X		X
Concomitant therapy and procedures recording	Must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAE reporting[e]	SAEs will be collected from signing of Informed Consent through 30 days after the last dose of study drug			
AE reporting[e]	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first			
SAMPLES AND LABORATORY ASSESSMENTS[c]				
Hematology[f] & serum chemistry	X[g]	X		X
Thyroid function test (TSH)	X			
Urinary phosphate[h]	To be performed as clinically indicated			
Vitamin D	To be performed as clinically indicated			
Bone marrow aspirate and biopsy	Will be considered for patients with recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion.			
Coagulation	See Section 7.4.16 and Section 7.4.19.1			
Pregnancy test[i]				X
Urinalysis (predose)	X			X
CCI [redacted]				

Table 1.16 ARM 5 (MLN2480 + Irinotecan): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES			End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 27 (± 2 days)	
DISEASE ASSESSMENT				
Disease evaluation, including CT or MRI scan[k]			X	X
STUDY DRUG DOSING				
MLN2480 dosing[l]	MLN2480 dosing: Days 2, 9, 16, and 23			
Irinotecan dosing[l]	Irinotecan infusion: Days 1 and 15			

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI [redacted]; C*x*D*x* = Cycle *x*, Day *x*; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a Includes documentation of any suspicious lesions. Need not be repeated if the prior assessment was performed within 72 hours. See Section 7.4.7.

b Predose (within 15 minutes before dosing).

c When the timing of a blood sample coincides with the timing of vital sign and ECG measurements, the vital signs and ECG will be completed first.

d To be performed on Cycle 2 Day 27, Cycle 4 Day 27, and every 4 cycles thereafter on Day 27 (ie, Cycle 8 Day 27, Cycle 12 Day 27), or as clinically indicated.

e A plasma sample to measure the concentration of MLN2480 and/or the combination agent should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

f If a patient develops ANC < 500/µL or platelet count < 25,000/µL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/µL and platelets return to > 50,000/µL.

g Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1. Samples for the Day 1 assessments for each cycle may be obtained up to 72 hours before the study visit.

h Spot urine phosphate measurements or 24-hour urine phosphate collection acceptable, as clinically indicated (see Table 6.14).

i For women of reproductive potential, only. EOS pregnancy test must be serum.

j CCI [redacted]

k Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 2 cycles beginning Cycle 2, Day 27 (± 2 days), and at the EOS visit. Disease assessments need not be repeated if performed within 4 weeks prior to the End of Study visit. See Section 7.4.20.

l Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 at home. See Sections 6.1.1 and 6.1.6 for additional dosing instructions for Arm 5.

Schedules of Events for Arm 6 (MLN2480 Monotherapy)

Table 1.17 ARM 6 (MLN2480 Monotherapy): Cycle 1 Schedule of Events

PROCEDURES*	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)			
		1	8	15	22
Informed consent form	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical history	X				
Physical examination (including height[a] and weight)	X	X	X	X	
Vital signs (temperature, blood pressure, heart rate)[b]	X	X	X	X	
ECHO or MUGA scan	X				
12-lead safety ECG[c]	X				
Patient diary review	X	X	X	X	X
ECOG performance status	X	X	X	X	X
Concomitant therapy & procedures recording	Concomitant therapy and procedures must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first				
SAE collection[d]	SAEs will be collected from the signing of Informed Consent through 30 days after the last dose of study drug				
AE reporting[d]	AEs will be recorded from the first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first				
SAMPLES AND LABORATORY ASSESSMENTS[b]					
Hematology[e] & serum chemistry	X	X[f]	X	X	X
Coagulation	X	See Section 7.4.16 and Section 7.4.19.1			
Pregnancy test[g]	X	X			
Urinalysis	X				

Table 1.17 ARM 6 (MLN2480 Monotherapy): Cycle 1 Schedule of Events

PROCEDURES*	Screening (≤ 28 days before Cycle 1, Day 1)	CYCLE 1, STUDY DAY (± 2 days)			
		1	8	15	22
CCI [redacted]					
Archival or fresh tumor biopsy[h]	X				
DISEASE ASSESSMENT					
Disease evaluation, including CT or MRI scan[i]	X				
STUDY DRUG DOSING					
MLN2480 dosing[j]		MLN2480 Q2D oral dosing: every other day, 28-day cycle			

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CCI [redacted] d; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic(s); Q2D = every other day; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

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

* PK may be collected at any time upon investigator request.

a Height is to be collected at screening only.

b When the timing of a blood sample coincides with the timing of vital sign measurements, the vital signs will be completed first.

c A single 12-lead ECG will be collected at screening in all patients to assess eligibility and at end of study.

d A plasma sample to measure the concentration of MLN2480 should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

e If a patient develops ANC < 500/μL or a platelet count < 25,000/μL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/μL and platelets return to > 50,000/μL.

f Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1.

g For women of reproductive potential, only. Screening pregnancy test must be serum. Either a urine or serum pregnancy test is permitted within 72 hours before the first dose of study drug.

h An archival tumor tissue block or 10 slides from the diagnostic biopsy or surgical specimen from the most recent diagnosis will be requested for all patients at screening. If the archived sample is unavailable or inadequate (eg, < 10 slides), a fresh biopsy may be required. The fresh biopsy specimens must be obtained at least 2 days after the last dose of any prior anticancer therapy and within 28 days before the first dose of study drug. See Section 7.4.19 and Section 7.4.19.1.

i 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. See Section 7.4.20.

j Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when a clinic visit is not scheduled, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.7 for dosing instructions for Arm 6.

Table 1.18 ARM 6 (MLN2480 Monotherapy): Cycles ≥ 2 Schedule of Events

PROCEDURES	CYCLE 2 AND SUBSEQUENT CYCLES		End of Study (EOS)
	Day 1 (± 2 days)	Day 15 (± 2 days)	
Physical examination & weight measurement	X		X
Vital signs (temperature, blood pressure, heart rate)[a]	X	X	X
12-lead safety ECG[b]			X
ECOG performance status	X		X
Patient diary review	X	X	X
Concomitant therapy and procedures recording	Must be recorded from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first		
SAE reporting[c]	SAEs will be collected from signing of informed consent through 30 days after the last dose of study drug		
AE reporting[c]	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first		
SAMPLES AND LABORATORY ASSESSMENTS[a]			
Hematology[d] & serum chemistry	X[e]	X	X
Coagulation	See Section 7.4.16 and Section 7.4.19.1		
Pregnancy test[f]			X
DISEASE ASSESSMENT			
Disease evaluation, including CT or MRI scan[g]	X		X
STUDY DRUG DOSING			
MLN2480 dosing[h]	MLN2480 oral dosing: every other day (28 day cycle)		

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

a When the timing of a blood sample coincides with the timing of vital sign measurements, the vital signs will be completed first.

b A single 12-lead ECG will be collected at end of study.

c A plasma sample to measure the concentration of MLN2480 should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged to be related to treatment, irrespective of the cycle or day of occurrence of the AE. See Section 7.4.18.

d If a patient develops ANC < 500/μL or platelet count < 25,000/μL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/μL and platelets return to > 50,000/μL.

e Hematology and serum chemistry results will be evaluated before the patient is allowed to initiate each cycle; see Section 7.4.16.1. Samples for the Day 1 assessments for each cycle may be obtained up to 72 hours before the study visit.

f For women of reproductive potential, only. EOS pregnancy tests must be serum.

g Disease response assessments (including CT or MRI scans of all sites of disease) by RECIST will be performed every 8 weeks beginning in Cycle 2 on Day 1 (± 2 days) of each cycle, and at the EOS visit. Disease assessments need not be repeated if performed within 4 weeks prior to the EOS visit. See Section 7.4.20.

h Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.7 for additional dosing instructions for Arm 6.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
alisertib	MLN8237
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine 5'triphosphate
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-inf}}$	area under the plasma concentration versus time curve from zero to infinity
$AUC_{0\text{-last}}$	area under the concentration time curve from time 0 to the time of last quantifiable concentration
$AUC_{0\text{-tau}}$	area under the plasma concentration versus time curve from zero to next dose
BID	*bis in die*; twice daily
BUN	blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CRO	contract research organization
CT	computed tomography
CCI	[redacted]
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency

Abbreviation	Term
EOS	End of Study (visit)
ERK	extracellular signal-regulated kinase
EU	European Union
FBG	fasting blood glucose
FDA	United States Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practices
H2	histamine-2
HbA1c	glycosylated hemoglobin
hERG	human ether-à-go-go related gene
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IUD	intrauterine device
IV	intravenous; intravenously
IXRs	Interactive voice/web response system
K_i	inhibition constant
LDH	lactate dehydrogenase
LFT	liver function test(s)
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK or extracellular signal-regulated kinase
MET	mesenchymal-epithelial transition factor
mCRC	metastatic colorectal cancer
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mechanistic (formerly mammalian) target of rapamycin

Abbreviation	Term
mTORC1	target of rapamycin complex 1
mTORC2	target of rapamycin complex 2
MUGA	multiple gated acquisition (scan)
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NPO	nothing by mouth
NSCLC	non small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
pERK	phosphorylated ERK
PFS	progression-free survival
P-gp	P-glycoprotein
PI3Kα	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
QD	*quaque die*; once daily
QOD	*quaque altera die*; every other day
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	once weekly
Q2W	every 2 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SPF	skin protection factor
SUSAR	suspected unexpected serious adverse events
TAK-580	new company name for MLN2480
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent AE
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
ULN	upper limit of the normal range
US	United States

Abbreviation	Term
USPI	United States package insert
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Study

This study will investigate MLN2480, administered in 5 separate combinations and 1 monotherapy cohort, ie, MLN2480 + MLN0128 (Arm 1), MLN2480+ alisertib [MLN8237] (Arm 2), or MLN2480 + paclitaxel (Arm 3) in patients with advanced solid (nonhematologic) tumors, with an Expansion phase in patients with non-small cell lung cancer to include MLN2480 monotherapy Q2D (Arm 6), or MLN2480 + cetuximab (Arm 4) or MLN2480 + irinotecan (Arm 5) in patients with advanced solid (nonhematologic) tumors, with an Expansion phase in patients with colorectal cancer.

1.1.2 Study Drugs

Unless otherwise noted, "study drug" refers to combination dosing of MLN2480 plus the respective combination agent (ie, MLN2480 + MLN0128, MLN2480 + alisertib, MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan). Properties of each of the individual agents are briefly described in the following sections.

1.1.2.1 MLN2480

MLN2480 is a potent, small molecule pan-RAF kinase inhibitor being developed for the treatment of solid tumors, both as a single agent and in combination with other agents. As a combination therapy, MLN2480 has the potential to support the inhibition of tumor cell signaling at multiple nodes. The RAF kinases (A-, B-, and C-RAF) are key components of the mitogen-activated protein kinase (MAPK) pathway that controls cell proliferation and survival signaling. The MAPK pathway, which is composed of RAS, RAF, MAPK kinase (MEK), and extracellular signal-regulated kinase (ERK), integrates signals from receptors on the cell surface including cancer-related receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR), mesenchymal epithelial transition factor (MET), and the vascular endothelial growth factor receptor (VEGFR). The MAPK pathway is frequently activated in human cancer by mutation of BRAF, NRAS, KRAS, or other pathway components. Recent approvals of BRAF and MEK small molecule inhibitors in melanoma have confirmed the importance of this pathway in cancer patients.

The ability of MLN2480 to inhibit both RAF monomer and dimer-mediated signaling is a key feature that distinguishes it from recently approved BRAF inhibitors (vemurafenib and

dabrafenib). MLN2480 is a potential first-in-class molecule with clinical attributes of both a RAF and MEK inhibitor. On the basis of nonclinical and preliminary clinical data to date, MLN2480 has an acceptable safety profile enabling a variety of combination approaches. Additional information regarding MLN2480 is provided in the MLN2480 Investigator's Brochure (IB).

1.1.2.2 MLN0128

MLN0128 is a novel, highly selective, orally bioavailable adenosine 5' triphosphate (ATP)-competitive inhibitor of the serine/threonine kinase referred to as the mechanistic target of rapamycin (mTOR). MLN0128 (formerly INK128) targets 2 distinct multiprotein complexes, mTORC1 and mTORC2.

MLN0128 is being developed both for oncology and non-oncology indications. For oncology patients, MLN0128 is being investigated as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or antihormonal agents. Non-oncology indications being investigated include fibrotic and inflammatory diseases in the lung or bronchioles such as idiopathic pulmonary fibrosis and bronchiolitis obliterans syndrome. MLN0128 is also being developed in combination with MLN1117 (an oral phosphoinositide-3-kinase alpha isoform inhibitor) as a treatment for advanced nonhematologic malignancies. Additional information regarding MLN0128 is provided in the MLN0128 IB.

1.1.2.3 Alisertib

Alisertib is a selective small molecule inhibitor of Aurora A kinase that is being developed as an oral treatment for advanced solid tumor malignancies and advanced hematological malignancies in single-agent and combination studies. Aurora A kinase is expressed in all actively dividing cells; it is localized to centrosomes and the proximal mitotic spindle during mitosis where it functions in a diverse set of mitotic processes. Given the essential role of mitosis in tumor proliferation, alisertib has the potential to be applied across a broad range of human tumors. It has demonstrated activity against a broad range of nonclinical tumor models and is expected to be toxic to proliferating normal tissues, such as the bone marrow and gastrointestinal epithelium. Additional information regarding alisertib is provided in the Alisertib IB.

1.1.2.4 Paclitaxel

Paclitaxel (a taxane) is an antimicrotubule agent approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of breast, ovarian, and non-small cell lung cancer. Paclitaxel promotes the assembly of microtubules from tubulin dimers, and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.[8] For more information, please see the US package insert (USPI) [9] or Summary of Product Characteristics (SmPC) [10] for paclitaxel.

1.1.2.5 Cetuximab

Cetuximab is an EGFR inhibitor indicated for the treatment of metastatic colorectal cancer (mCRC), metastatic non-small cell lung cancer, and squamous cell carcinoma of the head and neck. Specifically, cetuximab is approved for the treatment of patients with EGFR-expressing mCRC, in combination with chemotherapy, and as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. The positive opinion from the European regulatory agency, the Committee for Medicinal Products for Human Use (CHMP), was received for mCRC first-line use in May 2008. For more information, please see the SmPC for cetuximab [11].

1.1.2.6 Irinotecan

Irinotecan is an antineoplastic agent of the topoisomerase I inhibitor class, approved in many countries for use as first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum, and in patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. The initial New Drug Application (NDA) for irinotecan was approved in 1996. For more information, please see the SmPC for irinotecan [12].

1.2 Nonclinical Experience

1.2.1 MLN2480

In biochemical kinase inhibition assays, MLN2480 demonstrates potent inhibition of the oncogenic $BRAF^{V600E}$ mutant and the wild-type BRAF and CRAF kinases and inhibits a small subset of kinases in addition to RAF in a similar potency range. MLN2480 has shown

a high degree of selectivity in a large nonkinase screening panel of 169 receptors, transporters, and channels.

In vitro, MLN2480 inhibited phosphorylated ERK (pERK) signaling and/or cell proliferation in the majority of mutant and wild-type BRAF cell lines evaluated. In cell growth inhibition assays, MLN2480 inhibited MAPK pathway signaling in cells with mutant BRAF, which signals as a monomer, and some cells with RAS mutation, where RAF signals as a dimer. In vivo, a single oral dose of MLN2480 demonstrated strong and sustained suppression of pERK in mutant and wild-type BRAF mouse xenograft models. Significant antitumor activity was observed in multiple tumor xenograft models that had $BRAF^{V600E/D}$ mutations or were wild type for BRAF, including models of melanoma and colon, lung, and pancreatic cancer. MLN2480 exhibits the greatest overall antitumor activity in melanoma, colon, and lung cancer models. Collectively, the data provide strong rationale for conducting MLN2480 clinical trials in a variety of solid tumors.

Safety pharmacology studies in rats and monkeys did not identify any notable cardiovascular, central nervous system (CNS), or respiratory liabilities for MLN2480. The human protein binding is 97.5%, giving a free concentration of 0.19 μM at C_{max}. The potential for human ether-à-go-go related gene (hERG) inhibition is considered to be low. Additionally, there were no electrocardiogram (ECG) findings in 4-week repeat-dose studies in monkeys dosed every other day (QOD), up to and including 30-mg/kg MLN2480. In accordance with International Conference on Harmonisation (ICH) S9 guidelines and consistent with a drug at this stage in development for oncology indications, reproductive toxicity studies have not been conducted.

For more information, please see the MLN2480 IB.

1.2.2 MLN0128

In nonclinical oncology investigations, MLN0128 selectively and potently inhibits mTOR kinase (the IC_{50} [concentration inhibiting 50% of enzyme activity] is 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation. MLN0128 inhibited phosphorylation of downstream modulators of mTORC1and mTORC2 in human U87 glioblastoma tumor xenograft models in mice and showed strong tumor growth inhibition at tolerable oral doses in all 8 tested xenograft models.

MLN0128 has a low potential to affect the hERG potassium ion channel and did not affect cardiovascular parameters in vivo in telemeterized monkeys. The toxicologic profiles

obtained in Good Laboratory Practice (GLP)-compliant and non-GLP-compliant studies in rats and monkeys were generally consistent with pharmacologic inhibition of mTORC1/2 activity. There were no apparent sex differences in observed toxicities. Preliminary findings in ongoing rat and rabbit embryofetal studies indicated teratogenic, fetotoxic, and abortive effects with MLN0128. Embryofetal lethality and/or teratogenic effects have been reported with the TORC1 inhibitors rapamycin and the rapalogs.

Hyperglycemia and hyperinsulinemia are known toxicities associated with inhibition of mTOR and related pathways based on nonclinical studies. A rise in fasting plasma glucose has been observed as early as 1 to 2 days following oral administration of MLN0128.

For more information, please see the MLN0128 IB.

1.2.3 Alisertib

In nonclinical investigations, alisertib inhibited proliferation of a wide variety of tumor cell lines grown in culture and induced phenotypes consistent with Aurora A kinase inhibition, including mitotic spindle defects, mitotic delay, and apoptosis. In combination with standard–of–care agents administered in multiple tumor models, alisertib results in synergistic or additive antitumor effects.

Safety pharmacology studies with alisertib did not identify significant adverse effects in the CNS and cardiovascular systems at tolerated doses. Alisertib exhibited minimal activity against hERG current (IC_{50} and inhibition constant [K_i] > 100 μM), but did exhibit in vitro activity against the gamma aminobutyric acid A alpha-1 benzodiazepine binding site (K_i = 290 nM), and related effects were observed at nontolerated doses and/or exposures. Alisertib was negative for mutagenicity in the Ames assay and equivocal for clastogenicity in a rat bone marrow micronucleus assay.

For more information, please see the alisertib IB.

1.2.4 Paclitaxel

Paclitaxel is commercially available in the US and in Europe. For more information, please see the USPI [9] or SmPC [10].

1.2.5 Cetuximab

Cetuximab is commercially available in the US and Europe. For more information, please see the SmPC [11].

1.2.6 Irinotecan

Irinotecan is commercially available in the US and Europe. For more information, please see the SmPC [12].

1.3 Clinical Experience

1.3.1 MLN2480

MLN2480 is currently being evaluated as a single agent in one phase 1 study in patients with advanced solid tumors (excluding lymphoma). Preliminary data are available for a total of 181 patients. The emerging safety profile indicates that MLN2480 is generally well tolerated, with manageable adverse events (AEs) that are common with the RAF kinase inhibitor class of drugs. The AE of rash has been identified as an adverse drug reaction due to the observed incidence and known class effect of RAF-kinase inhibitors. Further details are provided in the MLN2480 IB.

1.3.2 MLN0128

As of a clinical data cutoff of 09 December 2013, MLN0128 was being investigated in 2 phase 1 studies in patients with advanced solid malignancies. A third phase 1 study had been completed in patients with hematologic malignancies. Across these open-label studies, a total of 274 patients had been enrolled and 248 had received at least 1 MLN0128 dose as of the cutoff date. In general, observed toxicities have been assessed primarily as severity Grade 1 or 2 and have been manageable with supportive care and/or dose interruption or reduction. A total of 15 deaths reported to the clinical database as of data cutoff had occurred within 30 days of the last study drug dose; of these 15 events, 1 (cardiac arrest) was considered related to MLN0128. Further details are provided in the MLN0128 IB.

1.3.3 Alisertib

As of 29 March 2014, alisertib was in phase 3 development and had been administered to a total of 1080 patients in clinical studies that are investigating alisertib as a single agent and in combination with other agents (paclitaxel, docetaxel, and rituximab ± vincristine). Alisertib has demonstrated objective responses in a variety of solid and hematologic malignancies. Using a treatment-free period for recovery between each cycle of drug administration, results from phase 1 and phase 2 studies indicate that the more frequent toxicities can be monitored by routine clinical evaluations and represent mechanistic effects in proliferating tissues (bone marrow, gastrointestinal [GI] epithelium, hair follicles). While the reversibility of alopecia has not been established, other prevalent toxicities

(myelotoxicities and GI disorders) are largely reversible and manageable by dose reduction, interruption of the dosing schedule, or supportive care. Further details are provided in the alisertib IB.

1.3.4 Paclitaxel

For clinical information regarding paclitaxel, please see the USPI [9] or SmPC [10].

1.3.5 Cetuximab

For clinical information regarding cetuximab, please see the SmPC [11].

1.3.6 Irinotecan

For clinical information regarding irinotecan, please see the SmPC [12].

1.4 Study Rationale

Each combination agent administered with MLN2480 in this study has been part of single-agent and combination clinical development programs. Support for investigating each combination treatment arm is provided in the subsections that follow. Additive combination activity has been observed in preclinical studies of MLN2480 administered in combination with MLN0128, alisertib, and taxanes.

1.4.1 MLN2480 + MLN0128 (Arm 1)

MLN0128 has dual activity against mTORC1 and mTORC2. mTOR is a key effector of the MAPK pathway in MAPK-dominant tumors.[13] The MAPK and PI3K signal transduction pathways are often co-activated in malignant cells.[14] Acquired resistance to inhibitors of 1 of these cell signaling pathways may be the result of activation of the other pathway.[15,16] Agents targeting the RAF and/or MEK pathways have shown synergy in combination with MLN0128 in diverse cell lines with broad mutation status and cancer indications. Please see the MLN0128 IB and the MLN2480 IB for more information.

1.4.2 MLN2480 +Alisertib (Arm 2)

Inhibition of the MAPK pathway leads to cell cycle arrest and, in some cases, apoptosis. Importantly, the MAPK pathway is also required for the deoxyribonucleic acid (DNA) replication or damage checkpoint responses.[17,18] Alisertib is an oral Aurora A kinase inhibitor. Aurora A kinase inhibition results in mitotic arrest leading directly to apoptosis or to abnormal mitotic divisions that in turn lead to cell death or arrest. However, a portion of

cells can recover from these outcomes and re-enter the cell cycle. This observation raises the possibility that MAPK pathway inhibition could affect cell survival subsequent to DNA damage caused by Aurora A kinase inhibition. Therefore, combining a MAPK pathway inhibitor with an Aurora A kinase inhibitor such as alisertib could lead to therapeutic activity that exceeds that of either agent administered alone. Interruption of MEK/ERK signaling is therefore predicted to amplify terminal outcomes from deleterious aneuploidy caused by Aurora A kinase inhibition. This theory was tested using trametinib (a MEK inhibitor and therefore MAPK pathway inhibitor, in lieu of MLN2480) plus alisertib. A synergistic effect was observed in assays combining trametinib with alisertib in melanoma and ovarian cancer cell models. MAPK pathway inhibition resulting from trametinib administration prevents the formation of cells with > 4N DNA content induced by alisertib, which leads to inhibition of cell-cycle progression and increases in cell death subsequent to abnormal mitosis. Enhanced antitumor activity with trametinib in combination with alisertib was also demonstrated in colon and ovarian cancer xenograft models. Please see the alisertib IB and the MLN2480 IB for more information.

1.4.3 MLN2480 + Paclitaxel (Arm 3)

MAPK signaling cascades are activated by several stimuli. Once activated, downstream activators of this pathway initiate transcriptional programs, thereby driving cell proliferation [19]. Inhibition of this pathway inhibits cell proliferation and in certain instances drives pro-apoptotic signaling or reduces the threshold for apoptosis induction by other agents. Commonly used chemotherapeutics—including DNA-damaging and microtubule-stabilizing agents—ultimately drive cell death but require cells to be in cycle for this to occur. Further, these agents have been shown to promote activation of several cell-survival pathways, including MAPK [20]. In preclinical studies, MEK inhibitors (used as surrogates for MLN2480) in combination with taxane agents have been shown to synergistically increase apoptosis of RAS- or RAF-mutant cell lines.[21] Clinical evidence suggests potential efficacy in combining MAPK pathway inhibitors such as selumetinib (a MEK1/MEK2 inhibitor, downstream of KRAS) with conventional chemotherapeutics such as docetaxel (a taxane). Proof-of-concept for administering a MAPK pathway inhibitor in combination with docetaxel was demonstrated in a prospective, randomized, phase 2 trial that assessed selumetinib plus docetaxel in previously treated patients with advanced KRAS-mutant non-small cell lung cancer [22]. These results support investigation of the combination of MLN2480 + paclitaxel (also a taxane) to possibly augment the efficacy of single-agent paclitaxel in patients with KRAS-mutant tumors or BRAF non-V600 mutation-

positive non-small cell lung cancer (NSCLC). Please see the MLN2480 IB for more information.

1.4.4 MLN2480 + Cetuximab (Arm 4)

Anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies are an effective therapy for a minority of patients with mCRC. An intrinsic mechanism of resistance to anti-EGFR therapy is dysregulation of the MAPK pathway which is common in mCRC. Up to 55% of colon cancers harbor a mutation in K-RAS or N-RAS with another 8% to 10% with B-RAF mutations [23-25]. Further, the clinical efficacy of EGFR targeted antibodies is limited by the development of acquired (secondary) resistance, which is often associated with activation (via new activating mutations or amplifications) of the MAPK pathway. Agents that molecularly target the MAPK pathway could potentially provide new treatment options for mCRC patients with intrinsic or acquired resistance to anti-EGFR therapy.

However, in contrast to the pronounced single agent-activity in melanoma, the single-agent activity of selective inhibitors of BRAF or MEK in mCRC has been limited [26]. Prahallad et al [27] investigated the limited single-agent activity of vemurafenib, an oral selective inhibitor of BRAF and found that BRAF inhibition leads to rapid upstream activation of EGFR with subsequent bypass signaling via the PI3K/Akt/mTOR pathway. The addition of an EGFR inhibitor to BRAF inhibition in the setting of BRAF mutant mCRC would therefore diminish this bypass effect and indeed, preclinical models of BRAF mutant CRC have demonstrated the anti-proliferative effects of an anti-EGFR with an anti-BRAF combination.

Clinical studies are now ongoing to evaluate the combination of MAPK pathway inhibition with EGFR inhibition in not only BRAF mutant disease but in mCRC harboring mutations or activation in KRAS (NCT02450656, “Afatinib and Selumetinib in Advanced KRAS Mutant and PIK3CA Wildtype Colorectal, Non-small Cell Lung and Pancreatic Cancer [M14AFS],” accessed 05 August 2015; NCT01750918, “BRAF/MEK/EGFR Inhibitor Combination Study in Colorectal Cancer [CRC],” accessed 05 August 2015). While the preliminary results are promising with partial responses observed in patients with KRAS mutant CRC [28], the limitations of MEK inhibitors generally, ie, the pharmacokinetics and safety profile and/or drug-mediated CRAF re-activation of the MAPK pathway, may reduce the therapeutic benefit of an anti-EGFR + MEKi combination.

As a pan-RAF inhibitor with a long half-life, MLN2480 could overcome the potential biological and pharmacological limitations of the MEK inhibition in mCRC. MLN2480

once-weekly (QW) may result in greater MAPK pathway inhibition than MEK inhibitors with better tolerability and without the potential for drug-induced CRAF re-activation of the MAPK pathway.

Arm 4 will test the hypothesis that MLN2480 in combination with the anti-EGFR monoclonal antibody cetuximab will demonstrate clinical benefit in patients with mCRC in the presence of MAPK pathway dysregulation (where anti-EGFR therapy may prevent bypass signaling via the PI3K/Akt/mTOR pathway), specifically those with BRAF V600 or non-canonical RAS mutation-positive disease.

1.4.5 MLN2480 + Irinotecan (Arm 5)

Cellular mechanisms causing irinotecan resistance have been reported for each step of the CPT-11 pathway [29]. The MAPK pathway has been implicated in the regulation of apoptosis as well as in the response to chemotherapeutic drugs [30].

Activation of MAPK by SN38, the active metabolite of irinotecan, has been observed in MCF-7 breast cancer cells [31] or in response to other chemotherapeutic agents such as 5-FU [32] or oxaliplatin [33]. Preclinical data suggest that the phosphorylation status of the MAPK p38α and β isoforms may be a marker of resistance to irinotecan-based chemotherapies in CRC [34]. These studies suggest the use of MAPK inhibitors as an adjuvant therapy may potentiate the efficacy of irinotecan-based chemotherapies in non-responder CRC patients.

Clinical studies to evaluate the combination of MEK inhibition with irinotecan in relapsed/refractory mCRC with MAPK pathway dysregulation (KRAS or BRAF mutation) are ongoing. While the preliminary results are promising with clinical benefit observed (PRs and prolonged SD) in patients with KRAS mutant CRC [35], the limitations of MEK inhibitors, as identified above could also adversely affect the potential benefit of an MEKi + irinotecan combination.

Arm 5 will test the hypothesis that MLN2480 in combination with irinotecan will demonstrate clinical benefit in patients with mCRC in the presence or absence of MAPK pathway dysregulation where MLN2480 may potentiate the clinical activity of irinotecan therapy.

1.4.6 MLN2480 Monotherapy Every Other Day (Arm 6)

MLN2480, administered orally QOD in cycles of 22 and 28 days, was evaluated in a phase 1, dose escalation trial in patients with advanced cancers and in expansion cohorts of patients with Stage 3 or 4 melanomas, divided according to tumor genotype and treatment history, as well as in a PK-expansion cohort of patients with advanced cancers. Doses in the dose escalation portion of the trial ranged from 20 to 280 mg. DLTs were observed in 2 patients at 280 mg given in a 22-day cycle (1 DLT of Grade 3 periorbital edema and 1 DLT of Grade 3 rash). A total of 80 patients were treated at the MTD of 200 mg given in a 28-day cycle, 20 in the PK and 60 in the melanoma expansion cohorts. The most frequently observed adverse events of all grades were rash (36%); fatigue (30%); anemia (26%); elevated CPK (25%); nausea (20%); myalgia, periorbital edema, and pruritus (18%); constipation (16%); and elevated AST (13%). The most frequently observed Grade 3 or higher events were rash (9%), anemia (8%), and increased fatigue, elevated CPK and elevated AST (3%). Overall, 50% of the 16 BRAF-mutated melanoma patients achieved a PR, with a median PFS of 4.6 months (range, 1.0-40.8) [36].

BRAF codes for a kinase in the MAP kinase pathway, and BRAF mutations can lead to activation of the MAPK pathway, although there are also rare mutations that are inactivating. BRAF mutations occur in between 3% and 5% of patients with NSCLC, mostly in patients with adenocarcinomas [1,2,4]. In various series, these mutations have been shown to exist independently, and tumors characterized by BRAF mutations generally do not demonstrate concomitant mutations in EGFR, ALK, or ROS [5]. Of these BRAF mutations, approximately half are V600 mutations, and the remainder are non-V600 mutations occurring primarily in exons 11 and 15 [1]. Although there are several agents that can inhibit the BRAF V600–derived kinase, these same agents are generally inactive against the non-V600 mutated kinases [1]. Data on outcomes for the V600 and the non-V600 BRAF mutations in NSCLC vary across different series, with some studies showing better survivals for the patients with V600 mutation and others demonstrating better survival in patients with the non-V600 mutations [1,2,4]; because all of these series include relatively small numbers of patients, any outcome data must be viewed highly critically.

MLN2480 was evaluated in vitro in NCI-H1666 cells harboring the G466V mutation and in NCI-H1755 cells harboring the G469A mutation. In these experiments, MLN2480 was associated with a paradoxical increase in phosphor-ERK within a narrow range of concentrations; there was no effect on the growth of the cells. Because of this, patients with these 2 mutations will be excluded from the study.

1.4.7 Rationale for Dosing Schedules and Starting Doses (Escalation Phase)

1.4.7.1 MLN2480

For all arms, study drug treatments will be administered in 28-day cycles. There are no readily apparent risks for clinically meaningful mutual pharmacokinetic (PK) drug-drug interactions (DDIs) between MLN2480 and the 5 agents selected to be combined with MLN2480, based on in vitro metabolism data and physiologically relevant exposures achieved at clinical single-agent doses. Therefore dose escalation up to the MLN2480 single-agent maximum tolerated dose (MTD) of 200 mg QOD or 600 mg once-weekly (QW) will occur as tolerated. Modifications to MLN2480 single agent MTD dosing schedule for each treatment arm is as follows:

Treatment Arms 1 to 3

During the Escalation phase, MLN2480 will be administered initially to all patients in Arms 1 to 3 according to a modified QOD schedule on Days 1, 3, and 5 of each week (ie, Day 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26), referred to throughout the protocol as "QOD schedule." The starting dose of 100 mg for MLN2480 is 50% below the unit dose of MLN2480 single-agent MTD (200 mg QOD in 28-day cycles) determined in clinical Study C28001 and is considered a safe starting dose in Arms 1 to 3. Should the dosing schedule of ≥ 160 mg QOD prove tolerable in Arm 3, the QW MLN2480 schedule may then be explored.

MLN2480 (400 mg or 600 mg) QW will initially be administered according to the same schedule to all patients in Arm 3: every week of each cycle on Days 2, 9, 16 and 23. The starting dose (400 mg or 600 mg) will depend on the MTD of MLN2480 identified by the QOD dosing schedule (ie, 600 mg QW approximates the exposure of 200 mg QOD). MLN2480 administration may be changed to less frequent dosing should the aforementioned schedule not be tolerated.

Treatment Arms 4 and 5

During the Escalation phase, MLN2480 will be initially administered to all patients in Arms 4 and 5, according to the QW schedule (ie, Days 2, 9, 16, and 23). The starting dose for MLN2480 will be 400 mg QW, which is 33% below the unit dose of MLN2480 single-agent MTD (600 mg QW in 28-day cycles) determined in clinical Study C28001. MLN2480 administration may be changed to a lower starting dose (ie, 300 mg QW) or a less frequent schedule (Days 2, 9, and 16) if a ≥ 400 mg QW MLN2480 dose (administered on Days 2, 9, 16, and 23 of each cycle) is not found to be tolerable in Arm 3 (MLN2480 + paclitaxel).

1.4.7.2 MLN0128

The combination dosing regimen for MLN0128 was selected for this study based on the observed safety and tolerability profile of MLN0128 in the single-agent clinical Study INK128-001. In Study INK128-001, no dose-limiting toxicities (DLTs) were observed with a schedule of 9-mg MLN0128 administered QD for 3 days followed by 4 days off each week (QD × 3d QW); thus 9 mg is considered the recommended phase 2 dose (RP2D) for single-agent MLN0128 under this schedule. The initial starting dose of 2 mg of MLN0128 (QD × 3d QW) represents 22% of the single-agent MLN0128 RP2D for this schedule.

1.4.7.3 Alisertib

The combination dosing regimen for alisertib was selected based on the observed safety and tolerability profile of alisertib when administered across many studies as a single agent and in combination. On the basis of these data, the alisertib 3-days on/4-days off for 3 weeks schedule was chosen for this study. The proposed initial starting dose of 30 mg of alisertib twice daily (BID) on this schedule is 1 dose level below (25% less than) the MTD of alisertib when given in combination with paclitaxel, which is a cytotoxic agent.

1.4.7.4 Paclitaxel

Paclitaxel will initially be given at the recommended dose [37-39] of 80 mg/m^2 QW on Days 1, 8, and 15 of each 28-day cycle. If exposures of MLN2480 are not achieved at MTD in combination with paclitaxel 80 mg/m^2, the paclitaxel dose may be de-escalated per institutional standard. Dose-dense weekly administration of paclitaxel is a proven strategy to further enhance antitumor activity, especially in the re-treatment setting. Preclinical and clinical studies have demonstrated that duration of paclitaxel exposure is an important determinant of its cytotoxic effect. Thus, cytotoxicity can be enhanced at fairly low concentrations of paclitaxel provided that the exposure is extended, eg, through weekly administration.[40-42]

1.4.7.5 Cetuximab

Treatment with cetuximab will commence at the recommended dose with a 400 mg/m^2 loading dose (Cycle 1 Day 1), then continue at 250 mg/m^2 QW (Days 8, 15, and 22 of Cycle 1; Days 1, 8, 15, and 22 of all cycles thereafter). If exposures of MLN2480 are not achieved at MTD in combination with cetuximab at 250 mg/m^2, the cetuximab dose may be de-escalated per institutional standard.

1.4.7.6 Irinotecan

Irinotecan will be administered at the recommended dose of a 180 mg/m^2 intravenous infusion over 30 to 90 minutes Q2W (Days 1 and 15). If exposures of MLN2480 are not achieved at MTD in combination with irinotecan at 180 mg/m^2, the irinotecan dose may be de-escalated per institutional standard.

1.4.8 Rationale for Pharmacokinetic Assessments

Clinical PK assessments conducted during the Escalation phase of the study will characterize the systemic exposures of the respective agents in a combination setting to verify the lack of clinically meaningful mutual DDIs, assess achievement of exposures, and contribute to exposure/toxicity relationship analyses of these combination treatment arms to support selection of the RP2Ds of the combinations. After analysis of preliminary Escalation data, up to 3 combination treatment arms and regimens will be selected for investigation in the Expansion phase.

In the Expansion phase, the effect of MLN2480 on the PK of the combination partner(s) will be evaluated in approximately 12 patients at the RP2D of each selected combination.

1.4.9 Rationale for Tumor Characterization

Archival tumor material (or fresh biopsy material, if archival material is unavailable) will be requested from all patients before their first dose of study drug, with the goal of broadly characterizing the factors underlying each patient's sensitivity/resistance to the respective treatment combination. In addition, an optional biopsy from patients who initially respond to study treatment and then relapse will be requested to identify the genetic underpinnings of resistance development.

While candidate biomarkers of sensitivity for MLN2480 (such as BRAF and NRAS mutations) have been identified, it is unclear from preclinical data obtained to date as to whether these mutations also predispose sensitivity to each of the combination agents (ie, with MLN0128, alisertib, paclitaxel, cetuximab, or irinotecan). Moreover, although mutations in phosphoinositide-3-kinase alpha isoform, phosphatase and tensin homolog, and the tumor suppressor complex-1/2 have been hypothesized to be sensitizing to mTOR inhibitors, no clear patient selection markers have been identified thus far for single-agent MLN0128, alisertib, paclitaxel, cetuximab, or irinotecan. The exploratory objective proposed for this study will attempt CCI [redacted]

CCI [redacted]

1.4.10 CCI [redacted]

CCI [redacted]

1.5 Potential Risks and Benefits

With the exception of MLN2480, each of the agents administered in this study have been administered to patients as a single agent and in combination with other treatments. MLN2480 has been administered to date as a single agent (see Section 1.3). This is the first study in which each of the specific combination treatment arms has been administered in humans. The emerging safety profile of each of the agents, including data from nonclinical and clinical studies, has been reviewed to determine potential overlapping toxicities that may be associated with each agent in the 5 Escalation combination treatment arms. A summary of the overlapping toxicities are discussed in the subsections that follow. Please see Section 1.4 for a discussion of the nonclinical evidence suggesting potential benefits associated with each of the combination treatment arms.

General risk mitigation strategies for potential AEs in this study include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent clinical and laboratory results monitoring, guidelines for management of potential toxicities, criteria for dose modification, criteria for determining DLTs, and regular monitoring of AEs and serious adverse events (SAEs) by the sponsor. Please see Section 6.8 for information on the management of a few of the clinical events that may occur in this study.

1.5.1 Potential Overlapping Toxicities and Drug-Drug Interaction Risk Assessments

1.5.1.1 MLN2480 + MLN0128 (Arm 1)

Based on review of preliminary single-agent clinical data, no major safety concerns were identified for the combination of MLN2480 + MLN0128. Potential overlapping toxicities of the combination include fatigue, rash, nausea, vomiting, diarrhea, and pruritus. These toxicities are expected to be manageable with adequate monitoring and standard care.

Based on rat and monkey toxicology studies (Study P024-09-03, Study P024-09-05, Study TX-003-2009, and TX-004-2009), nonclinical overlapping toxicities identified for the combination of MLN2480 + MLN0128 include effects on bone marrow, lymphoid, and GI tissue. Monkeys dosed with MLN0128 in 28-day GLP toxicology studies demonstrated skin effects. The potential for a substantial increase in toxicity was assessed by monitoring limited toxicology endpoints in nonclinical pharmacology studies of MLN2480 + MLN0128 combination therapy in mouse xenograft models.

In general, administration of MLN0128 + MLN2480 at doses associated with significant antitumor activity was tolerated, with marked transient decreases in body weight (< 15%) that recovered during the treatment period and end of study (body weight loss of < 7%). However, 1 mouse out of 6 treated with MLN2480 (50 mg/kg twice weekly) + MLN0128 (3 mg/kg QW) was found dead on Day 9. This mouse had 21.7% body weight loss, and the cause of death may be related to the combination treatment. The other 5 mice in the MLN2480 (50 mg/kg twice weekly) + MLN0128 (3 mg/kg QW) dose group survived to the scheduled necropsy with acceptable decreases in body weight. There are no major safety concerns based on these nonclinical assessments, and toxicities are expected to be manageable and will be monitored in the clinic.

In vitro, MLN2480 and MLN0128 are metabolized by multiple cytochrome P450s (CYPs). MLN0128 is metabolized by CYP2C19, CYP3A4, and CYP2C9. In addition, MLN2480 is metabolized by aldehyde oxidase. MLN2480 and MLN0128 are not expected to produce clinically meaningful inhibition or induction of major CYP enzymes at clinical doses based on in vitro and clinical PK data. Based on these data, there are no readily apparent risks for clinically meaningful mutual PK DDIs between MLN2480 and MLN0128 when administered in combination.

Please see the MLN0128 IB and the MLN2480 IB for more information.

1.5.1.2 MLN2480 + Alisertib (Arm 2)

Based on review of preliminary single-agent clinical data, no major safety concerns were identified for the combination of MLN2480 + alisertib. Potential overlapping toxicities include anemia/decreased hemoglobin, nausea, diarrhea, vomiting, fatigue, and rash. These toxicities are expected to be manageable with adequate monitoring and standard care.

Based on rat, dog, and monkey toxicology studies, nonclinical overlapping toxicities identified for the combination of MLN2480 + alisertib include effects on bone marrow and lymphoid tissue. The potential for a substantial increase in toxicity was assessed by monitoring limited toxicology endpoints in the nonclinical pharmacology studies of the MLN2480 + MLN8237 combination in mouse xenograft models. In general, administration of MLN2480 + MLN8237 at doses associated with significant antitumor activity was tolerated, with marked transient decreases in body weight (< 9%) that recovered during the treatment period (Study MLP-132). There are no major safety concerns based on this nonclinical assessment and toxicities are expected to be manageable and will be monitored in the clinic.

In vitro, MLN2480 is metabolized by aldehyde oxidase and multiple CYPs. Alisertib is metabolized by CYP3A (major) and glucuronidation, based on preliminary results from human ADME (absorption, distribution, metabolism, excretion) and follow-up in vitro investigations. The systemic exposure of alisertib may be altered by moderate and strong inhibitors of CYP3A4 and clinically significant enzyme inducers. Based on in vitro and clinical PK data, MLN2480 and alisertib are not expected to produce clinically meaningful inhibition or induction of major CYP enzymes at clinical doses. Although alisertib is a weak inhibitor of P-glycoprotein (P-gp), MLN2480 is not a P-gp substrate and therefore DDI via P-gp inhibition is not anticipated. These data suggest that there are no readily apparent risks for clinically meaningful mutual PK DDIs between MLN2480 and alisertib when administered in combination.

Please see the alisertib IB and the MLN2480 IB for more information.

1.5.1.3 MLN2480 + Paclitaxel (Arm 3)

Based on review of preliminary single-agent clinical data, no major safety concerns were identified for the combination of MLN2480 + paclitaxel. Potential overlapping toxicities of the combination include anemia/decreased hemoglobin, nausea, diarrhea, vomiting, and

arthralgia/myalgia. These toxicities are expected to be manageable with adequate monitoring and standard care.

Nonclinical overlapping toxicities identified for the combination of MLN2480 + paclitaxel include effects on bone marrow and lymphoid tissue. The potential for a substantial increase in toxicity was assessed by monitoring limited toxicology endpoints in the nonclinical pharmacology studies of therapy with MLN2480 + docetaxel in mouse xenograft models. (Docetaxel was used as a surrogate for paclitaxel.) In general, administration of MLN2480 + docetaxel at doses associated with significant antitumor activity was tolerated, with marked decreases in body weight (< 17%; Study MLP-132). There are no major safety concerns based on these nonclinical assessments, and toxicities are expected to be manageable and will be monitored in the clinic.

In vitro, MLN2480 is metabolized by aldehyde oxidase and multiple CYPs. Paclitaxel is metabolized by CYP2C8 and CYP3A, and is a substrate of P-gp. Based on in vitro and clinical PK data, MLN2480 is not expected to produce clinically meaningful inhibition or induction of major CYP enzymes at clinical doses. Paclitaxel is not reported to be a clinically meaningful perpetrator of metabolic/transporter-based DDIs. Taken together, there are no readily apparent risks for clinically meaningful mutual PK DDIs between MLN2480 and paclitaxel when administered in combination.

Refer to the USPI [9]or SmPC [10] for paclitaxel for information regarding potential risks and benefits of treatment with this medication.

1.5.1.4 MLN2480 + Cetuximab (Arm 4)

Based on review of preliminary single-agent clinical data, no major safety concerns were identified for the combination of MLN2480 + cetuximab. Potential overlapping toxicities of the combination include rash, pruritus, fatigue, and GI toxicities including constipation, diarrhea, and vomiting. These toxicities are expected to be manageable with adequate monitoring and standard care.

In vitro, MLN2480 is metabolized by aldehyde oxidase and multiple CYPs. Based on in vitro and clinical PK data, MLN2480 is not expected to produce clinically meaningful inhibition or induction of major CYP enzymes at clinical doses. Cetuximab is not reported to be a clinically meaningful perpetrator of metabolic/transporter-based DDIs. Taken together, there are no readily apparent risks for clinically meaningful mutual PK DDIs between MLN2480 and cetuximab when administered in combination.

Refer to the SmPC for cetuximab [11] for information regarding potential risks and benefits of treatment with this medication.

1.5.1.5 MLN2480 + Irinotecan (Arm 5)

Based on review of preliminary single-agent clinical data, no major safety concerns were identified for the combination of MLN2480 + irinotecan. Potential overlapping toxicities of the combination include rash, anemia/decreased hemoglobin, fatigue, pyrexia, and GI toxicities including nausea, vomiting, diarrhea, and constipation. These toxicities are expected to be manageable with adequate monitoring and standard care.

As mentioned in Section 1.5.1.4, MLN2480 is not expected to produce clinically meaningful inhibition or induction of major CYP enzymes at clinical doses. Irinotecan is metabolized by CYP3A4/5 [44]. In addition, irinotecan is activated by hydrolysis to SN-38, an inhibitor of topoisomerase I. Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) converts SN-38 to inactive SN-38 glucuronide. The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes. Taken together, there are no readily apparent risks for clinically meaningful mutual PK DDIs between MLN2480 and irinotecan when administered in combination.

Refer to the SmPC for irinotecan [12] for information regarding potential risks and benefits of treatment with this medication.

1.5.1.6 MLN2480 QOD Monotherapy (Arm 6)

As this is an MLN2480 QOD monotherapy arm, there are no safety concerns regarding overlapping toxicities.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives are:

- **To determine the safety** profile and the MTDs/potential RP2Ds of the combination treatments of MLN2480 + MLN0128, MLN2480 + alisertib, MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan in patients with advanced nonhematologic malignancies

- To determine the safety profile and RP2D of the combination treatments of MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan

2.2 Secondary Objectives

The secondary objectives are:

- To characterize plasma PK of MLN2480 + MLN0128, MLN2480 + alisertib, MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan upon co-administration in each combination setting

- To evaluate preliminary efficacy as measured by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)

2.3 Exploratory Objectives

The exploratory objective is:

CCI

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoints are:

- Safety and tolerability, including incidence of AEs and SAEs

- DLTs, MTDs, and RP2Ds for each arm

3.2 Secondary Endpoints

The secondary endpoints are:

- PK parameters for MLN2480, MLN0128, and alisertib including but not limited to maximum (peak) concentration (C_{max}), first time of occurrence of maximum (peak) concentration (T_{max}), area under the concentration time curve from time 0 to the end

of the dosing interval ($AUC_{0\text{-}tau}$); paclitaxel, cetuximab, and irinotecan PK parameters including, but not limited to C_{max}, area under the concentration time curve from time 0 to the time of last quantifiable concentration ($AUC_{0\text{-}last}$), area under the concentration time curve from time 0 to infinity ($AUC_{0\text{-}inf}$), and half-life ($t_{1/2}$)

- Measures of disease response including objective response rate (ORR), duration of response (DOR), time to response, progression-free survival (PFS) based on the investigator's assessment using RECIST (version 1.1) criteria

3.3 Exploratory Endpoint

The exploratory endpoint is:

CCI

4. STUDY DESIGN

4.1 Overview of Study Design

This is an open-label, multicenter, phase 1b study that incorporates a Dose Escalation (Escalation) phase and a Dose Expansion (Expansion) phase. The study will enroll adult patients with advanced, solid (nonhematologic) malignancies and who, in the opinion of the treating physician, have failed standard therapies and for whom a phase 1 trial is an appropriate option.

The Escalation phase will investigate 5 combination arms (ie, MLN2480 + MLN0128, MLN2480 + alisertib, MLN2480 + paclitaxel, MLN2480 + cetuximab, and MLN2480 + irinotecan). This study is the first to administer these combinations to humans.

Once the maximum tolerated dose (MTD) for each combination treatment arm has been established in the Escalation phase, up to 3 combination treatment arms and regimens will be evaluated in the Expansion phase based on tolerability and exposure data collected during Escalation. The combination of MLN2480 + paclitaxel will be administered to patients with KRAS exon 2 or BRAF non-V600 mutation-positive NSCLC who are naïve to previous treatment with RAF or MEK inhibitors. The combination of MLN2480 + cetuximab will be administered to patients with BRAF V600 or non-canonical RAS mutation-positive mCRC.

Finally, the combination of MLN2480 + irinotecan will be administered to patients with previously treated mCRC who are naïve to previous treatment with RAF or MEK inhibitors. Finally, MLN2480 will be administered QOD to patients with NSCLC with non-V600 BRAF mutations.

Throughout the study, AEs, SAEs, laboratory values, vital signs, physical examination findings, ECOG performance status, and ECGs will be obtained to evaluate the combination treatment arms. 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.[45] Dose-limiting toxicities (DLTs) are defined in Section 6.2. Study drug may be discontinued if a patient experiences study treatment-related toxicity.

Serial blood samples to measure plasma concentrations of MLN2480 and the respective combination agents will be collected during Cycle 1 at prespecified time points as indicated in the respective Schedules of Events table and described in Section 7.4.18. Underlying disease status will be assessed by the investigator per RECIST (version 1.1) using radiological evaluations (computed axial tomography [CT] scan or magnetic resonance imaging [MRI], as clinically indicated). In both study phases, CCI [redacted] Doing so will enable understanding of the mechanisms associated with sensitivity and resistance to the drug combinations.

Patients may choose to discontinue therapy at any time. Patients will attend an End of Study visit 30 (+ 10) days after receiving their last dose of study drug.

4.2 Number of Patients

Approximately 125 patients were originally planned for this study. As of this Amendment 6, 81 patients have been enrolled (several treatment arms were not completely enrolled). Evaluable patients will be enrolled in this study from approximately 10 to 15 study centers in the US and Europe. Of these patients, approximately 49 will be enrolled in the Escalation phase (ie, approximately 4 for Arm 1; approximately 15 for Arm 2; approximately 18 for Arm 3; approximately 6 for Arm 4; approximately 6 for Arm 5). Approximately 76 to 88 patients will be enrolled in the Expansion phase (approximately 16 for Arm 3, approximately 30 for Arm 4, approximately 30 for Arm 5, and approximately 12 for Arm 6). Because a 3 + 3 dose escalation design will be used, the actual sample size will depend upon the number of dose escalation steps and number of patients required per cohort. Patients enrolled into the Escalation phase are not eligible to participate in the Expansion phase. Up

to an additional 33 patients may be enrolled in the current treatment arm of patients with NSCLC and non-V600 BRAF mutations for a total of 114 patients.

4.3 Duration of Study

Patients will participate in the Screening and Treatment periods. During screening, patient eligibility for the study will be determined within 28 days before Cycle 1, Day 1. During the Treatment period, patients will take their assigned study drug combination in 28-day treatment cycles until they experience disease progression, an unacceptable toxicity occurs, or the patient discontinues for any other reason. Treatment in any patient will not exceed 12 cycles without prior consultation with the sponsor. Patients who tolerate treatment and have evidence of clinical benefit after 12 cycles in the opinion of the investigator may continue treatment with continued monitoring upon prior review and approval by the project clinician.

Each patient will attend an End of Study visit 30 days (+ 10 days) after his/her last study drug dose, or the start of subsequent anticancer therapy, whichever occurs first, to permit the detection of any delayed treatment-related AEs.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

<u>All treatment arms:</u>

1. Male or female patients 18 years or older.
2. Patients who, in the opinion of the treating physician, have failed standard therapies and for whom a phase 1 trial is an appropriate option.
3. Radiographically or clinically evaluable tumor. ***For Expansion phase***: Tumors must be measurable as defined by RECIST (version 1.1).[46], and of the protocol-specified genetic mutational status, where applicable.
4. Recovered (ie, ≤ Grade 1 toxicity) from adverse effects (except alopecia) of prior therapy.

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Section 14.1).

6. Expected survival time of at least 3 months in the opinion of the investigator.

7. Block of banked tumor tissue and/or ≥ 10 unstained slides. Patients who satisfy all other eligibility criteria but do not have banked tissue/slides may be asked to consent to baseline biopsy.

8. Suitable venous access for the study-required blood sampling, including PK sampling.

9. Thyroid function tests consistent with stable thyroid function.
   Note: Patients on a stable dose of thyroid replacement therapy for a suggested minimum of 12 weeks before Cycle 1, Day 1 are eligible.

10. Clinical laboratory values as specified below before first dose of study drug:

    - Absolute neutrophil count (ANC) ≥ 1500/mm^3, platelet count ≥ 100,000/mm^3, and hemoglobin ≥ 9 g/dL. (Note: Blood transfusions are allowed up to 2 weeks before the Cycle 1, Day 1 dose.)

    - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) or < 2 × ULN if Gilbert's disease is known to be the only underlying hepatic disorder.

    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN range (AST and ALT ≤ 2.5 × ULN if liver function test [LFT] elevations are due to liver metastases).

    - Creatinine clearance ≥ 30 mL/min (≥ 50 mL/min for MLN0128 arm), based either on Cockcroft-Gault estimate (see Section 14.3) or on a 12- or 24-hour urine collection.

11. Left ventricular ejection fraction (LVEF) of 50% or greater, as measured by echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan, within 28 days before the first dose of MLN2480.

12. Must be able to swallow and retain oral medication.

13. 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 120 days (4 months) after the last dose of study drug for patients in Arms 1, 2, and 5, and through 6 months for patients in Arms 3 and 4, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (4 months) after the last dose of study drug for patients in Arms 1, 2, and 5, and through 6 months for patients in Arms 3 and 4, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

14. 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.

15. Additional inclusion requirements for Arm 1 ONLY (MLN2480 + MLN0128):

a. Metabolic fasting glucose ≤ 130 mg/dL and fasting triglycerides ≤ 300 mg/dL.

b. Creatinine clearance ≥ 50 mL/min, based either on Cockcroft-Gault estimate (see Section 14.3) or on a 12- or 24-hour urine collection.

16. Additional inclusion criteria for Arm 3 Expansion Only (MLN2480 + paclitaxel)

a. Patients with KRAS exon 2 or BRAF non-V600 mutation-positive NSCLC who have received a minimum of 1 but not more than 2 prior cytotoxic-approved regimens.

17. Additional inclusion criteria for Arm 4 Expansion Only (MLN2480 + cetuximab)

a. Patients with BRAF V600 or non-canonical RAS mutation-positive mCRC who have received a minimum of 1 but not more than 2 prior cytotoxic-approved regimens. Non-canonical RAS mutations include mutations in KRAS or NRAS non-exon 2 (exon 3 or 4 mutations) or NRAS exon 2.

18. Additional inclusion criteria for Arm 5 Expansion Only (MLN2480 + irinotecan)

a. Patients with mCRC who have received a minimum of 1 but not more than 2 prior cytotoxic-approved regimens.

19. Additional inclusion criteria for Arm 6 Expansion Only (MLN2480)

a. Patients with NSCLC who are EGFR, ALK, and ROS negative and have received a minimum of 2 regimens, including a platinum-based regimen and a PD-1/PD-L1 directed agent, unless otherwise contraindicated, and whose tumors harbor non-V600 BRAF mutations, except for the G466V and G469A mutations.

5.2 Exclusion Criteria

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

<u>All treatment arms</u>:

1. Female patients who are lactating and breastfeeding, or have a positive serum pregnancy test during the Screening period and on Cycle 1, Day 1.

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

3. History of uncontrolled brain metastasis ***unless***: previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery; stable disease for ≥ 60 days without steroid use (or stable steroid dose established for ≥ 28 days before the first dose of MLN2480).

4. Ongoing seizure disorder or a requirement for antiepileptics.

5. Recent prior therapies, including: chemotherapy and hormonal therapy ≤ 4 weeks or 4 half-lives, whichever occurs first, before administration of study drug; immunotherapy/monoclonal antibody use ≤ 4 weeks before administration of MLN2480; or radiation therapy ≤ 3 weeks before administration of study drug.

6. Chronic therapeutic corticosteroid use with the exception of replacement therapy for adrenal insufficiency or corticosteroid inhalers. Premedication with corticosteroids per institutional standard of care is allowed.

7. History of any of the following ≤ 6 months before first dose: congestive heart failure, unstable angina, myocardial infarction, unstable symptomatic ischemic heart disease, uncontrolled hypertension (ie, systolic blood pressure > 160 mm Hg, diastolic blood pressure > 95 mmHg) despite appropriate medical therapy, any ongoing cardiac arrhythmias of > Grade 2 (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia), thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy). ***Exception***: Chronic, stable atrial fibrillation on stable anticoagulant therapy is allowed, including low molecular-weight heparin.

8. Known GI disease or prior GI procedure that could interfere with the oral absorption or tolerance of the respective combination agents.

9. Other clinically significant comorbidities or any other condition that could compromise study participation.

10. Known history of human immunodeficiency virus infection, hepatitis B, or hepatitis C; testing not required in absence of clinical findings or suspicion. Prior allogeneic bone marrow or organ transplantation, or active condition of chronic immune suppression is not allowed.

11. Concomitant use, or administration ≤ 14 days before first dose of study drug(s), of clinically significant enzyme inducers; see Section 14.4.

12. Treatment with gemfibrozil (strong CYP2C8 inhibitor) within 14 days before the first dose of MLN2480.

13. History of or current illicit drug use, drug abuse, or alcohol abuse.

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

15. **Additional exclusion criteria for Arms 3, 5, and 6 Expansion Only (MLN2480 + paclitaxel; MLN2480 + irinotecan; MLN2480 monotherapy):**

    a. Prior treatment with RAF, MEK, or other inhibitors of the MAPK pathway.

16. **Additional exclusion criteria for Arm 1 Only (MLN2480 + MLN0128):**

    a. Use of strong inhibitors of CYP3A, CYP2C9, or CYP2C19 within 14 days of the first dose of MLN0128, or patients who require treatment with these agents during the study; see Section 14.4.

    b. Medical conditions requiring regular use of proton pump inhibitors (PPIs) within 5 days preceding the first dose of MLN0128, or histamine-2 (H2)-receptor antagonists within 24 hours of the first dose of MLN0128, or patients who require treatment with these agents during the study.

    c. Poorly controlled diabetes mellitus defined as glycosylated hemoglobin (HbA1c) > 7%.

    d. History of any of the following ≤ 6 months before the first dose of MLN0128:

       - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures
       - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures
       - Requirement for inotropic support (excluding digoxin)
       - Placement of a pacemaker for control of rhythm

- New York Heart Association Class III or IV heart failure (see Section 14.2)

e. Significant active cardiovascular or pulmonary disease before first MLN0128 dose, including:

- Uncontrolled asthma or oxygen saturation < 90% by arterial blood gas analysis or pulse oximetry on room air
- Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention; or history of valve replacement
- Medically significant (symptomatic) bradycardia
- History of arrhythmia requiring an implantable cardiac defibrillator
- Baseline prolongation of the rate-corrected QT interval (QTc; eg, repeated demonstration of QTc interval > 480 ms per Fridericia correction [ie, $QT/(RR)^{0.33}$], or history of congenital long QT syndrome, or torsades de pointes)

f. Initiation of treatment with hematopoietic growth factors, or systemic corticosteroids (either intravenous [IV] or oral steroids, excluding inhalers) ≤ 1 week before the first dose of MLN0128 (patients already receiving erythropoietin on a chronic basis for ≥ 4 weeks are eligible).

17. Additional exclusion criteria for Arm 2 Only (MLN2480 + alisertib):

a. Use of strong or moderate CYP3A inhibitors ≤ 14 days of the first dose of alisertib

b. Medical conditions requiring regular use of PPIs within 5 days preceding the first dose of alisertib, or H2-receptor antagonists within 24 hours of the first dose of alisertib, or patients who require treatment with these agents during the study.

c. History of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness, such as severe chronic obstructive pulmonary disease.

18. **Additional exclusion criteria for Arm 3 Only (MLN2480 + paclitaxel)**

    a. Known hypersensitivity to paclitaxel or its components or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

19. **Additional exclusion criteria for Arm 5 Only (MLN2480 + irinotecan)**

    a. Use of strong or moderate CYP3A inhibitors ≤ 14 days of the first dose of irinotecan.

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).

Millennium-sponsored drug product will be provided to the study sites. Commercially available paclitaxel, cetuximab, and irinotecan will be procured or distributed according to the Pharmacy Manual.

Study drugs will be administered in 28-day cycles (all arms and both the Escalation and the Expansion phases). During the Escalation phase, MLN2480 will initially be administered according to the schedules outlined in the protocol, but may be changed to less frequent dosing should the initial schedule not be tolerated.

Eligible patients will report to the study site to receive their respective study treatment on days specified in the corresponding Schedules of Events. On dosing days when the patient does not have a clinic visit, patients will take their assigned oral study drug dose (ie, MLN2480, MLN0128, and alisertib, as applicable) at home. Patients should be encouraged to take their doses at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. Patients will be instructed to record in their dosing diary each dose they take. Patients should also record the occurrence of emesis and any missed doses in their dosing diaries and resume dosing at the next scheduled time with the prescribed dose. All missed doses or doses administered within approximately 1 hour before a vomiting episode should be recorded in the electronic case report form (eCRF).

A missed dose of MLN2480 should be taken within 12 hours (or within 24 hours for QW dosing only) or otherwise should be skipped, and the next dose should be taken as scheduled. A missed dose of MLN0128 or alisertib should be taken within 6 hours or should otherwise be skipped, and the next dose should be taken as scheduled. Any skipped dose should be considered a missed dose. Doses should not be doubled-up or repeated to make up for missed doses; instead, patients should resume dosing at the next scheduled time with the prescribed dose. If severe emesis or mucositis prevents the patient from taking a scheduled dose, the dose will not be re-administered and will be skipped.

For information regarding excluded concomitant medications for each arm, refer to Section 6.5 and the Pharmacy Manual. Refer to Section 6.11, Section 6.12, and Section 6.13 for details on the preparation, dispensation, storage, handling, disposal, and accountability of the study drug agents.

6.1.1 MLN2480 Administration (All Arms)

In the Escalation phase, MLN2480 (100, 160, or 200 mg) will be administered initially according to the same schedule to all patients in Arms 1 to 3 on Days 1, 3, and 5 of each week (ie, Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) in each 28-day cycle. Combination dosing schedules are provided in Table 6.1 (Arm 1), Table 6.2 (Arm 2), and Table 6.3 (Arm 3). In Arms 3 to 5, a QW dose of MLN2480 (400 or 600 mg) will be administered on Days 2, 9, 16, and 23 of each 28-day cycle. Combination dosing schedule for the QW dosing is provided in Table 6.3 (Arm 3), Table 6.4 (Arm 4), and Table 6.5 (Arm 5). For the QOD monotherapy expansion cohort, MLN2480 will be administered on Days 1, 3, 5, 7, etc, of each 28-day treatment cycle (14 doses) at a dose of 200 mg/day. The dosing schedule for QOD dosing is provided in Table 6.6 (Arm 6).

For all arms, MLN2480 will be given on an empty stomach with patients remaining NPO (nothing by mouth) except for water and prescribed medications for 2 hours before and 1 hour after each dose. Patients should take their MLN2480 tablets with approximately 8 ounces (1 cup, 240 mL) of water on dosing days. If emesis occurs after taking study drug, symptoms should be managed with standard antiemetic therapy; a repeat (replacement) dose of study drug should not be taken.

6.1.2 MLN2480 + MLN0128 (Arm 1)

During the Escalation phase for Arm 1, the starting dose for MLN2480 will be 100 mg. MLN2480 will be administered on Days 1, 3, and 5 of each week (ie, Days 1, 3, 5, 8, 10, 12,

15, 17, 19, 22, 24, and 26) in each 28-day cycle. The starting dose of 2-mg MLN0128 will be given for 3-days-on/4-days-off each week (ie, Days 2-4, 9-11, 16-18, and 23-25) in 28-day cycles.

MLN2480 and MLN0128 will be concomitantly administered on Days 3, 10, 17, and 24 of each cycle. As described in Section 7.4.16.2, daily fasting glucose measurements are required for Arm 1 in Cycles 1 and 2. On the concomitant dosing days during Cycles 1 and 2, patients will fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) before the scheduled dosing time and will perform their daily fasting glucose assessment as usual. They will then take their assigned MLN2480 and MLN0128 doses as described in Table 6.1 and Section 6.1.1. One hour later, they will eat a light meal. Starting with Cycle 3, MLN0128 will be taken on an empty stomach with patients remaining NPO except for water and prescribed medications for 2 hours before and 1 hour after each dose. Overnight (8 hour) fasting is required in Cycle 3 only on the evenings before scheduled clinic visits to facilitate fasting glucose measurements by the study staff. Additional fasting glucose measurements will be conducted as clinically indicated for each patient.

Dose escalation for Arm 1 will proceed as described in Section 6.3 and Section 6.3.1.

Table 6.1 Dosing Schedule for ARM 1 (MLN2480 + MLN0128)

	Study Day (All Cycles)																											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
MLN2480	X		X		X			X		X		X			X		X		X			X		X		X		
MLN0128		X	X	X					X	X	X					X	X	X					X	X	X			

On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 and of MLN0128 at home.
See Section 6.1.1 and Section 6.1.2 for additional dosing and fasting instructions for Arm 1.

6.1.3 MLN2480 + Alisertib (Arm 2)

During the Escalation phase for Arm 2, the starting dose for MLN2480 will be 100 mg. MLN2480 will be administered on Days 1, 3, and 5 of each week (ie, Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) in each 28-day cycle. The starting dose of 30-mg BID alisertib will be administered on Days 1-3, 8-10, and 15-17 in each 28-day cycle. MLN2480 and alisertib will be concomitantly administered on the mornings of Days 1, 3, 8, 10, 15, and 17 of each cycle. Dose escalation will proceed as described in Section 6.3 and Section 6.3.2.

During Cycle 1, alisertib will be administered at the clinic on an empty stomach, with patients remaining NPO except for water and prescribed medications for 2 hours before and 1 hour after the alisertib dose. During Cycle 2 and beyond, patients will be instructed to take each oral dose of alisertib with 8 ounces (1 cup, 240 mL) of water without regards to the timing of food intake.

Table 6.2 Dosing Schedule for ARM 2 (MLN2480 + Alisertib)

	Study Day (All Cycles)																											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
MLN2480	X		X		X			X		X		X			X		X		X			X		X		X		
Alisertib (BID)	X	X	X					X	X	X					X	X	X											

On dosing days when the patient does not have a clinic visit, patients will take their doses of MLN2480 and alisertib at home.

See Section 6.1.1 and Section 6.1.3 for additional fasting and dosing instructions for Arm 2.

6.1.4 MLN2480 + Paclitaxel (Arm 3)

During the Escalation phase for Arm 3, the starting dose for MLN2480 QOD is 100 mg. MLN2480 will be administered on Days 1, 3, and 5 of each week (ie, Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) in each 28-day cycle. For QW dosing, MLN2480 will be administered on Days 2, 9, 16, and 23. The starting dose (400 or 600 mg) will depend on the MTD dose of MLN2480 identified by the QOD dosing schedule (ie, 600 mg QW approximates the exposure of 200 mg QOD). Paclitaxel (80 mg/m^2) will be administered QW as a 1-hour IV infusion for 3 weeks (ie, Days 1, 8, and 15) in each 28-day cycle. MLN2480 and paclitaxel will be concomitantly administered on Days 1, 8, and 15 for all patients in Arm 3 receiving MLN2480 on the QOD schedule. On days when MLN2480 QOD and paclitaxel are concomitantly administered and a PK assessment is scheduled (see Table 1.8), MLN2480 should be administered 1 hour before the start of the paclitaxel infusion.

Dose escalation will proceed as described in Section 6.3 and Section 6.3.3. Paclitaxel can be de-escalated per institutional standard if exposure of MLN2480 is not achieved at MTD when combined with paclitaxel at 80 mg/m^2. The investigator will refer to the current product label for the most recent instructions on paclitaxel drug handling, administration, risks, and potential side effects. The MLN2480 dose found safe in this safety lead-in will be the dose used in combination with paclitaxel in the Expansion phase.

Table 6.3 Dosing Schedule for ARM 3 (MLN2480 + Paclitaxel)

	Study Day (All Cycles)																										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
MLN2480 (QOD Schedule)	X		X		X			X		X		X			X		X		X			X		X		X		
MLN2480 (QW Schedule)		X							X							X							X					
Paclitaxel	X							X							X													

Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.4 for additional dosing instructions for Arm 3.

Premedication for Paclitaxel-Associated Hypersensitivity or Other Acute Reactions

Premedication to prevent paclitaxel-associated reactions (hypersensitivity or other) is recommended according to institutional guidelines or local practices. Brief administration of H2 antagonists (eg, a single dose of cimetidine or ranitidine) is allowed if required on the day of paclitaxel administration. Modifications to paclitaxel administration or to premedications are allowed.

6.1.5 MLN2480 + Cetuximab (Arm 4)

Administration of MLN2480 will first be tested in combination with cetuximab at 400 mg QW on Days 2, 9, 16, and 23. Cetuximab will be administered IV at a loading dose of 400 mg/m^2 (Cycle 1 Day 1), then at 250 mg/m^2 QW on Days 8, 15, and 22 of Cycle 1 and Days 1, 8, 15, and 22 in each additional 28-day cycle.

Dose escalation will proceed as described in Section 6.3.4. Should MLN2480 given 400 mg QW be found safe, consideration will be given to test 600 mg QW. Cetuximab can be de-escalated per institutional standard if exposure of MLN2480 is not achieved at MTD when combined with cetuximab at 250 mg/m^2. The investigator will refer to the current product label for the most recent instructions on cetuximab drug handling, administration, risks, and potential side effects**.**

The MLN2480 dose found safe in this safety lead-in will be the dose used in combination with cetuximab in the Expansion phase.

Table 6.4 Dosing Schedule for ARM 4 (MLN2480 + Cetuximab)

	Study Day (All Cycles)																										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
MLN2480		X							X							X							X					
Cetuximab	X							X							X							X					

Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.5 for additional dosing instructions for Arm 4.

Premedication is recommended according to institutional guidelines or local practices.

6.1.6 MLN2480 + Irinotecan (Arm 5)

Administration of MLN2480 will first be tested in combination with irinotecan at 400 mg QW on Days 2, 9, 16, and 23. Irinotecan will be administered at 180 mg/m^2 via IV infusion over 30 to 90 minutes Q2W (Days 1 and 15).

Dose escalation will proceed as described in Section 6.3.5. Should MLN2480 given 400 mg QW be found safe, consideration will be given to test 600 mg QW. Irinotecan can be de-escalated per institutional standard if exposure of MLN2480 is not achieved at MTD when combined with irinotecan at 180 mg/m^2. The investigator will refer to the current product label for the most recent instructions on irinotecan drug handling, administration, risks, and potential side effects.

The MLN2480 dose found safe in this safety lead-in will be the dose used in combination with irinotecan in the Expansion phase.

Table 6.5 Dosing Schedule for ARM 5 (MLN2480 + Irinotecan)

	Study Day (All Cycles)																											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
MLN2480		X							X							X							X					
Irinotecan	X														X													

Patients will fast (with the exception of water) for at least 2 hours before and at least 1 hour after taking their MLN2480 dose. On dosing days when the patient does not have a clinic visit, patients will take their dose of MLN2480 at home. See Section 6.1.1 and Section 6.1.6 for additional dosing instructions for Arm 5.

Premedication is recommended according to institutional guidelines or local practices.

6.1.7 MLN2480 in Non-V600 BRAF NSCLC QOD (Arm 6)

Administration of MLN2480 will be tested in patients with NSCLC and non-V600 BRAF mutations as part of an expansion cohort. MLN2480 will be administered as an oral dose of 200 mg QOD. Each treatment cycle will consist of 28 days (14 doses). This is the recommended phase 2 dose of QOD MLN2480 as determined in Study C28001 (additional information on this dosing regimen may be found in the IB).

Table 6.6 Dosing Schedule for ARM 6 (MLN2480 Monotherapy)

	Study Day (All Cycles)																											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
MLN2480	X		X		X		X		X		X		X		X		X		X		X		X		X		X	

On dosing days when the patient does not have a clinic visit, patients will take their oral dose of MLN2480 at home.
See Section 6.1.1 and Section 6.1.7 for additional dosing and fasting instructions for Arm 6.

6.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010.[45] These criteria are provided in the Study Manual.

A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with MLN2480, MLN0128, alisertib, paclitaxel, cetuximab, or irinotecan:

- Any AE Grade 3 or higher that is assessed as at least possibly related to study drug with the exceptions noted below.

- Delay in the initiation of Cycle 2 due to a lack of adequate recovery from treatment-related toxicity (recovery to ≤ Grade 1 or to the patient's baseline, or to a level considered acceptable by the investigator after discussion with the project clinician) of ≥ 2 weeks due to hematologic toxicity believed to be unrelated to tumor infiltration; bone marrow evaluation may be required.

Exceptions:

Hematologic toxicities, including:

- Grade 4 neutropenia lasting < 7 days in duration in the absence of fever > 38.5°C sustained for > 1 hour

- Grade 3 neutropenia in the absence of fever > 38.5°C sustained for > 1 hour

Nonhematologic toxicities:

- Nausea, vomiting, and diarrhea will be considered DLTs only if they persist at ≥ Grade 3 for > 3 days despite adequate supportive care measures. At the investigator's discretion, patients who experience nausea, vomiting, or diarrhea after taking study drug may receive antiemetic or antidiarrheal medication before subsequent doses of study drug. Exception for patients receiving MLN0128: antiemetic drugs that are associated with a risk for QT prolongation (including ondansetron) will not be administered. The use of palonosetron is acceptable.

- Isolated ≥ Grade 3 laboratory abnormalities that resolve to ≤ Grade 1 in ≤ 7 days without clinical sequelae or need for therapeutic intervention will not be considered a DLT.

- Fatigue of severity Grade 3 lasting for ≤ 7 days will not be considered a DLT.
- Asymptomatic elevation of creatine phosphokinase will not be considered a DLT.
- Asymptomatic hypophosphatemia (< Grade 4) will not be considered a DLT.

Although DLTs may occur at any point during treatment, only those DLTs occurring during Cycle 1 will influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored throughout all cycles of therapy for treatment-related toxicities.

6.3 Dose Escalation Rules

In the Dose Escalation phase, MLN2480 will initially be administered, according to the schedules indicated, to patients in each combination arm. One cycle will consist of 28 days in each arm. The first 3 patients in Arm 1 (MLN2480 + MLN0128) will receive the MLN0128 starting dose of 2 mg on the days indicated in Table 6.1. The first 3 patients in Arm 2 (MLN2480 + alisertib) will receive the alisertib starting dose of 30 mg BID on the days indicated in Table 6.2. The first 3 patients in Arm 3 (MLN2480 + paclitaxel) will receive paclitaxel (80 mg/m^2 QW) on the days indicated in Table 6.3. The first 3 patients in Arm 4 (MLN2480 + cetuximab) will receive cetuximab (400/250 mg/m^2 QW) on the days indicated in Table 6.4. The first 3 patients in Arm 5 (MLN2480 + irinotecan) will receive irinotecan (180 mg/m^2 every 2 weeks [Q2W]) on the days indicated in Table 6.5.

A modified 3 + 3 dose escalation design will be used concurrently across the 5 combination arms. An End-of-Cohort meeting scheduled by the sponsor will occur after the last patient in each cohort in the Dose Escalation phase has completed the first treatment cycle/DLT observation period (ie, Day 1 to Day 28) for careful assessment of AEs, before escalating to the next dose. Pending the documented outcome of this meeting, doses will be escalated according to the following rules.

Starting with the treatment of 3 patients at the planned dose levels described previously, the dose intervals for each treatment arm will follow the 3 + 3 traditional escalation rules:

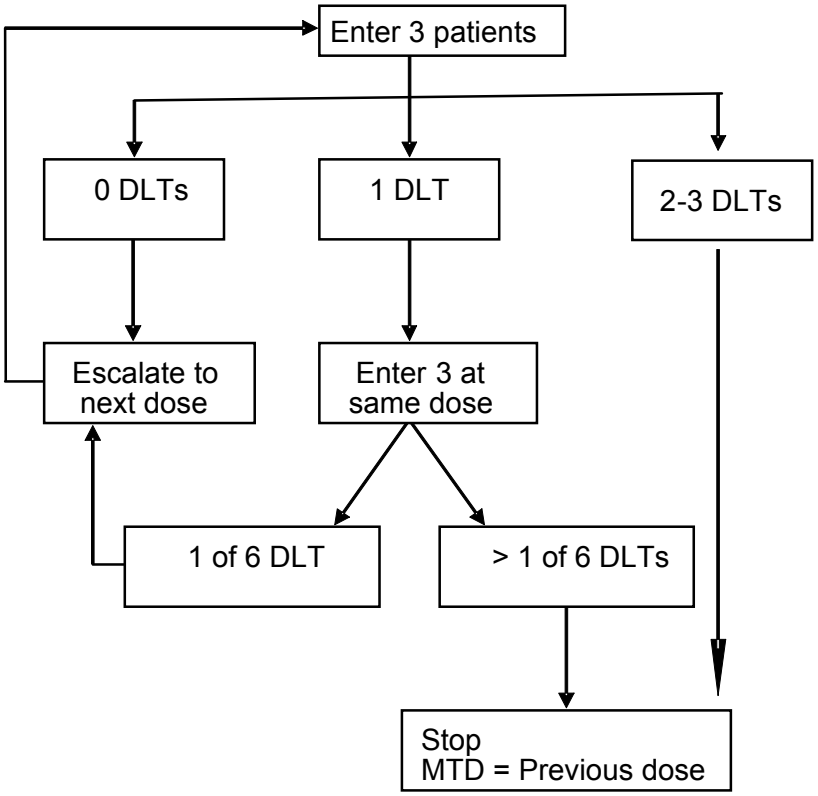
1. If 0 of 3 patients experiences DLT, dose escalation will proceed to the next higher dose level at which 3 patients will be enrolled.
2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.

3. Escalation will continue if 1 of 6 patients experiences DLT.

4. If 2 or more patients in any dose level experience DLT, dosing will stop, and the previous dose level will be considered the MTD.

Figure 6-1 is a diagrammatical representation of these rules.

Figure 6-1 Dose Escalation Algorithm



Patients in a given arm who do not receive at least 75% of all doses of both of their assigned treatment combination in Cycle 1 for reasons other than DLTs will be replaced within the treatment arm. Patients who experience a DLT may be allowed to continue treatment with the study drugs at a dose level below that which was associated with the DLT.

For MLN2480, dose escalation will proceed according to Table 6.7. The specific dose escalation strategy for each combination arm is described in the subsections that follow.

Table 6.7 MLN2480: Planned Escalation Dose Levels (ARMS 1 to 3[a])

Dose Level	Dose Increase Factor	Dose (mg)
1	Starting dose	100
2	60%	160
3	25%	200

More conservative dose escalation, evaluation of intermediate doses, modification of the dosing schedule, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of MLN2480 when given in combination.

a MLN2480 QOD dosing for Arm 3.

6.3.1 MLN2480 + MLN0128 (Arm 1)

In the MLN2480 + MLN0128 arm, MLN2480 will be escalated first, starting with 3 patients receiving 100 mg of MLN2480 in combination with MLN0128 (2 mg). As tolerability allows, MLN2480 doses will then be escalated according to Table 6.7, up to a maximum dose of 200 mg.

Should the 200-mg MLN2480 dose prove tolerable in this combination, MLN0128 will then be escalated according to Table 6.8, up to a maximum of 9 mg. More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of MLN0128 when given in combination.

Once the initial MTD of MLN2480 + MLN0128 has been reached, the potential to explore the safety of other combination doses within the range of the MTD for this arm may be examined.

Table 6.8 MLN0128: Planned Escalation Dose Levels

Dose Level[a]	Dose Increase Factor	Dose (mg)
1	Starting dose	2
2	100%	4
3	50%	6
4	50%	9

a More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible.

6.3.2 MLN2480 + Alisertib (Arm 2)

In the MLN2480 + alisertib arm, alisertib will be escalated first, with the first 3 patients receiving the starting dose of alisertib 30 mg BID in combination with MLN2480 (100 mg). As tolerability allows, alisertib will be escalated as indicated in Table 6.9 up 1 level, to 40 mg BID. Should the 40-mg BID alisertib dose prove tolerable, MLN2480 will then be escalated according to Table 6.7, up to 200 mg of MLN2480. Should the 200-mg MLN2480 dose in this combination prove tolerable, alisertib will then be escalated again to 50 mg BID. Once the initial MTD of MLN2480 + alisertib combination has been reached, the potential to explore the safety of other doses within the range of the combination MTD for this arm may be examined.

Table 6.9 Alisertib: Planned Escalation Dose Levels

Dose Level	Dose Increase Factor	Dose (mg BID)
1	Starting dose	30
2	33%	40
3	25%	50

Abbreviation: BID = twice daily.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of alisertib when given in combination.

6.3.3 MLN2480 + Paclitaxel (Arm 3)

In the MLN2480 + paclitaxel arm (QOD dosing), only MLN2480 will be escalated, starting with 3 patients receiving 100 mg of MLN2480 QOD in combination with paclitaxel (80 mg/m^2). Should this combination prove tolerable, MLN2480 will be escalated according to Table 6.7, up to the single-agent MLN2480 MTD of 200 mg QOD.

Once the MTD of the combination has been established with MLN2480 on the QOD (Day 1, 3, and 5) schedule, a QW MLN2480 dose will be explored beginning with a 3+3 safety lead-in. As shown in Table 6.10. The starting dose of MLN2480 will be 400 mg QW if the MTD combination MLN2480 is 160 mg on Days 1, 3, and 5, and the dose will be 600 mg QW (no escalation) if the MTD combination of MLN2480 is 200 mg on Days 1, 3, and 5. Should QW dosing of MLN2480 given in combination with paclitaxel prove unsafe, the Arm 3 expansion cohort will be dosed at the MTD on Days 1, 3, and 5.

Table 6.10 MLN2480: Planned Escalation Dose Levels (QW Dosing)

Dose Level	Dose Increase Factor	Dose (mg)	Dose Increase Factor	Dose (mg)
1	Starting dose	400	Starting dose	600
2	50%	600	N/A	N/A

N/A = not applicable

Paclitaxel can be de-escalated per institutional standard if exposure of MLN2480 is not achieved at MTD when combined with paclitaxel at 80 mg/m^2.

6.3.4 MLN2480 + Cetuximab (Arm 4)

The MLN2480 QW dose will be determined with a 3+3 safety lead-in as shown in Table 6.11. The starting dose of MLN2480 will be 400 mg QW. Should the 400 mg QW dose be found safe, the 600 mg QW dose may be tested.

Table 6.11 MLN2480: Planned Escalation Dose Levels (QW Dosing) for Arm 4

Dose Level	Dose Increase Factor	Dose (mg)
1	Starting dose	400
2	50%	600

Cetuximab can be de-escalated per institutional standard if exposure of MLN2480 is not achieved at MTD when combined with cetuximab at 250 mg/m^2.

6.3.5 MLN2480 + Irinotecan (Arm 5)

The MLN2480 QW dose will be determined with a 3+3 safety lead-in as shown in Table 6.12. The starting dose of MLN2480 will be 400 mg QW. Should the 400 mg QW dose be found safe, the 600 mg QW dose may be tested.

Table 6.12 MLN2480: Planned Escalation Dose Levels (QW Dosing) for Arm 5

Dose Level	Dose Increase Factor	Dose (mg)
1	Starting dose	400
2	50%	600

Irinotecan can be de-escalated per institutional standard if exposure of MLN2480 is not achieved at MTD when combined with irinotecan at 180 mg/m^2.

6.4 Dose Modification Guidelines

6.4.1 Intrapatient Dose Escalation

To provide patients the opportunity to derive maximum clinical benefit from study drug, patients in the dose escalation cohorts that are receiving treatment below the MTD/RP2D may be allowed to dose escalate provided that, during the most recent cycle, there have been no nonhematologic AEs ≥ Grade 2 related to the study drug combination, no dose interruptions related to study drug toxicities, and no delays of > 1 week in starting a cycle due to study drug toxicities. For a patient to escalate to the next dose level, the level above the proposed escalated dose must first be deemed safe; for hematologic and chemistry result requirements, see Section 7.4.16.1.

The sponsor, in collaboration with the investigators, will determine on a case-by-case basis whether intrapatient dose escalation is appropriate. Patients who have had any dose reductions will not be permitted to dose re-escalate.

6.4.2 Dose-Modification Guidelines (Dose Delays, Reductions, and Interruptions)

6.4.2.1 Dose Escalation

Any patient in the Dose Escalation phase whose toxicity meets a criterion of a DLT will discontinue study treatment. In some cases, the dose of study treatment may be reduced, following discussion between the investigator and the sponsor.

- If the patient experiences Grade 3 or 4 fatigue, the patient will stop taking study drug. The patient may resume taking the original dose of study drug if the fatigue resolves to ≤ Grade 1 within 7 days. Patients in the Dose Escalation phase will discontinue study treatment if they experience fatigue that resolves to ≤ Grade 1 in > 7 days.

- If the patient experiences an asymptomatic laboratory abnormality as outlined in Section 6.2, the patient will stop taking study drug. The patient may resume taking the original dose of study drug if the laboratory abnormality resolves to ≤ Grade 1 within 7 days. Patients in the Dose Escalation phase will discontinue study treatment if they experience an asymptomatic laboratory abnormality that resolves to ≤ Grade 1 in > 7 days.

- If the patient experiences a ≥ Grade 3 AE, the patient will stop taking study drug. If the AE resolves to ≤ Grade 2 in ≤ 14 days, the patient can resume taking study drug.

If the AE does not resolve to ≤ Grade 2 after 14 days, the patient must discontinue study treatment.

6.4.2.2 Dose Expansion

In the case of an individual patient experiencing an event meeting the definition of a DLT during any cycle, treatment will be delayed until toxicity is reduced to ≤ Grade 1 or the patient's baseline. For hematologic events, see Section 7.4.16.1.

When a dose modification is warranted for safety and the toxicity is thought to be attributable to MLN2480, the investigator should first consider reductions for the MLN2480 dose, if appropriate. Depending on the nature and severity of the AE, and under discretion of the investigator with agreement from the sponsor, the following dose modifications are recommended:

- Patients in the combination arms who experience a Grade 2 related AE may have their MLN2480 dose decreased by 1 dose level. Patients in the monotherapy arm may have their MLN2480 dose decreased to 160 mg.

- Patients in the combination arms who experience a Grade 3 related AE may have their MLN2480 dose decreased by 1 dose level. Patients in the monotherapy arm may have their MLN2480 dose decreased to 160 mg.

- Patients who experience an AE ≥ Grade 3 (regardless of relatedness to MLN2480) may stop taking MLN2480. If MLN2480 is held and the AE subsequently resolves to ≤ Grade 2 in ≤ 14 days, the patient can resume taking MLN2480 either at the original dose or a reduced dose, per investigator and sponsor discretion. If the AE does not resolve to ≤ Grade 2 after 14 days, the patient must discontinue study treatment.

The sponsor must be notified of any MLN2480 dose modifications.

Dose modification of MLN0128, alisertib, paclitaxel, cetuximab, or irinotecan may also be considered for events judged by the investigator to be directly related to these agents; see Section 6.8 for information on the management of particular clinical events. If there is no apparent clarity then both agents should be reduced. Doses will be reduced to the prior dose level as indicated in the appropriate table in Section 6.3 (for paclitaxel, cetuximab, or irinotecan, reduce per institutional standard). Patients can have a maximum of 2 dose modifications (if applicable) of MLN2480, MLN0128, or alisertib, as appropriate.

Reductions below dose level 1 (the starting dose) are not permitted for any drug with QOD dosing (see Section 6.3). Reductions below 300 mg QW for MLN2480 are not allowed. Dose reductions in a patient for any event will be permanent and will apply for all subsequent cycles (ie, once a dose has been reduced, it cannot be re-escalated to a higher dose). Patients who require > 2 dose modifications will be discontinued from the study.

The sponsor must be notified of any study drug dose modifications.

6.5 Excluded Concomitant Medications, Foods, and Procedures

6.5.1 All Arms

As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored because potential DDIs between MLN2480 and other drugs—including the agents in the combination treatment arms—have not been studied in humans. Patients should be instructed to consult with the investigator before taking any new medications, including any over-the-counter products.

Concurrent anticancer therapy or any other investigational therapy is not permitted during this study.

Use of clinically significant enzyme inducers and strong CYP2C8 inhibitors (eg, gemfibrozil) is prohibited within 14 days before the first dose of MLN2480 and throughout the study. The project clinician should first be consulted if a patient requires treatment during the study with 1 or more of the clinically significant enzyme inducers and/or strong CYP2C8 inhibitors. See Section 14.4 for a nonexhaustive list of clinically significant enzyme inducers and strong CYP2C8 inhibitors.

6.5.2 MLN0128

The following medications/therapies, and foods are prohibited during the study for patients receiving MLN2480 + MLN0128:

- Other investigational agents or mTOR inhibitors.
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of an MLN0128-related AE (eg, rash).
- Antiepileptic drugs for patients with a history of treated brain metastasis.

- Antiemetic drugs that are associated with a risk for QT prolongation, including ondansetron.

- Strong or moderate CYP3A inhibitors, strong CYP2C9 or CYP2C19 inhibitors within 14 days of the first dose of MLN0128 and throughout the study. Patients should not consume food or beverages containing the fruit or juices listed in Section 14.4 within 1 week before first dose of MLN0128 and throughout the study.

- Daily, chronic, or regular use of any PPI within 5 days before the first dose of MLN0128, or histamine-2 [H2]-receptor antagonists within 24 hours of the first dose of MLN0128. Neutralizing antacids should be avoided for 2 hours before and 2 hours after MLN0128 dosing.

6.5.3 Alisertib

The following medications/therapies are prohibited or restricted for patients receiving MLN2480 + alisertib, as described in the following.

- Because of alisertib's structural and pharmacological similarity to the benzodiazepines, concomitant therapy with benzodiazepines is discouraged but not prohibited. It is recommended that the use of any medication with potential CNS effects is minimized to avoid confusion in the interpretation of CNS effects should they occur during the course of treatment with alisertib.

- Daily, chronic, or regular use of any PPI 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). Antacid preparations are not permitted for 2 hours before or 2 hours after administration of the alisertib dose.

- The use of moderate or strong CYP3A inhibitors within 14 days before the first dose of alisertib or throughout the study; see Section 14.4 for a list of CYP3A inhibitors. Systemic 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 clinical practice standards; doses of anticoagulants should be adjusted or held in the setting of thrombocytopenia to mitigate the risk of bleeding.

6.5.4 Paclitaxel

Please refer to the paclitaxel USPI [9]or SmPC [10] for information on medications that are prohibited in patients receiving paclitaxel.

6.5.5 Cetuximab

Please refer to the cetuximab SmPC [11] for information on medications that are prohibited in patients receiving cetuximab.

6.5.6 Irinotecan

Please refer to the irinotecan SmPC [12] for information on medications that are prohibited in patients receiving irinotecan.

6.6 Permitted Concomitant Medications and Procedures

6.6.1 Medications Permitted in Patients Receiving Alisertib

Antiemetic agents may be administered at the discretion of the investigator. Prophylactic antiemetic agents can be used in the first cycle of treatment and in subsequent cycles according to standard clinical practice. All other manifestations of the patient's malignancy should be treated at the discretion of the investigator.

Systemic 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 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, 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. Medications such as typical or atypical antipsychotic and antidepressant agents are permitted.

6.6.2 Medications Permitted in Patients Receiving Paclitaxel

Premedication with corticosteroids, diphenhydramine, or H2-receptor antagonists is permitted before each treatment with paclitaxel.

6.6.3 Medications Permitted in Patients Receiving Cetuximab

Premedication is recommended according to institutional guidelines or local practices.

6.6.4 Medications Permitted in Patients Receiving Irinotecan

Premedication is recommended according to institutional guidelines or local practices.

6.7 Precautions and Restrictions

6.7.1 All Arms

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.

All patients must use effective contraception as described in the eligibility criteria and in Section 6.7.1.1.

Rashes (maculopapular, dermatitis acneiform, and pruritus) have been observed with MLN2480 administration.

Photosensitivity is a recognized class effect of RAF kinase inhibitors. Patients should avoid excess exposure to sunlight and use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) > 15.

6.7.1.1 Contraception Requirements

It is not known what effects any of the combination treatment arms 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 in the following.

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 120 days (4 months) after the last dose of study drug for patients in Arms 1, 2, and 5, and through 6 months after the last dose of study drug for patients in Arms 3 and 4. The 2 methods of contraception must include 1 highly effective method and 1 additional effective (barrier) method.

The following are examples of highly effective and additional effective methods of contraception.

Highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Condom
- Diaphragm
- Cervical cap

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Female patients must also agree not to donate ova (egg cells) during participation in the study or for 120 days (4 months) after the last dose of study drug for patients in Arms 1, 2, and 5, and for 6 months after the last dose of study drug for patients in Arms 3 and 4.

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 120 days (4 months) after the last dose of study drug for patients in Arms 1,2, and 5, and through 6 months after the last dose of study drug for patients in Arms 3 and 4, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

Male patients must also agree not to donate sperm during participation in the study or for 120 days (4 months) following the last dose of study drug for patients in Arms 1, 2, and 5, and for 6 months following the last dose of study drug for patients in Arms 3 and 4.

6.7.2 Paclitaxel

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

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

Please refer to the paclitaxel USPI [9]or SmPC [10] for additional information on precautions and restrictions associated with paclitaxel administration.

6.7.3 Cetuximab

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of cetuximab included rapid onset of airway obstruction, hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in 2% to 5% of 1373 patients in clinical trials, with a fatal outcome in 1 patient. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Therefore patients should be monitored for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae, and hypertrichosis occurred in patients receiving cetuximab therapy. Acneform rash occurred in 76% to 88% of 1373 patients receiving cetuximab in clinical trials. Severe acneform rash occurred in 1% to 17% of patients.

Acneform rash usually developed within the first 2 weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Monitor patients receiving cetuximab for dermatologic toxicities and infectious sequelae. Patients should be instructed to limit sun exposure during cetuximab therapy.

Please refer to the cetuximab SmPC [11] for additional information on precautions and restrictions associated with cetuximab administration.

6.7.4 Irinotecan

Irinotecan is emetogenic. It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT3 blocker (eg, ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of irinotecan. Physicians should also consider providing patients with an antiemetic regimen (eg, prochlorperazine) for subsequent use as needed.

Please refer to the irinotecan SmPC [12] for additional information on precautions and restrictions associated with irinotecan administration.

6.8 Management of Clinical Events

6.8.1 All Arms

6.8.1.1 Ocular Disturbances

An eye exam will be performed by an ophthalmologist if visual abnormalities are described by the patient. Careful monitoring of eye complaints should be followed. Patients must be instructed to report visual symptoms as soon as they occur. Early and aggressive management of mild visual symptoms may avoid more serious ocular complications.

6.8.1.2 Increased Creatine Kinase Levels

Increased creatine kinase levels have been observed with MLN2480 administration. While an increase in creatine kinase level alone (asymptomatic) is not reason to reduce the dose of MLN2480, it is important to rule out an accompanying clinical condition. See the recommendations in Table 6.13.

Table 6.13 Management of MLN2480-Associated Elevated Creatine Kinase Levels

AE Severity	Event Definition	Recommendation
Grade 1	> ULN to 2.5 × ULN	• Rule out increased physical activity, trauma, falls, muscle injury • Rule out concomitant use of statins or excessive environmental and other causes (eg, alcohol, drugs, toxins, heat illness, seizures, etc) • Adequate hydration is recommended to maintain fluid and electrolyte balance and tissue perfusion
Grade 2	> 2.5 × ULN to 5 × ULN	• Rule out increased physical activity, trauma, falls, muscle injury • Rule out concomitant use of statins or excessive environmental or other causes (eg, alcohol, drugs, toxins, heat illness, seizures, etc) • BUN, creatinine, urinalysis • Myoglobin test in urine (urine, heme +, RBC -) NOTE: Consider reducing dose of MLN2480 by 1 dose level.
Grade 3 Grade 4	> 5 × ULN to 10 × ULN > 10 × ULN	• Rule out increased physical activity, trauma, falls, muscle injury • Rule out concomitant use of statins or excessive environmental causes or other causes (eg, alcohol, drugs, toxins, heat illness, seizures, etc) • BUN, creatinine, urinalysis • Myoglobin test in urine (urine, heme +, RBCs) • In the presence of chest pain, test levels of Troponin I or Troponin T NOTE: Consider holding MLN2480 administration until value has decreased to Grade 1 or baseline.

Source: Common Terminology Criteria for Adverse Events (CTCAE), v4.03.[45]
Abbreviations: BUN = blood urea nitrogen; RBC(s) = red blood cell(s); ULN = upper limit of the normal range.

6.8.1.3 Decreased Phosphate Levels

Asymptomatic decreased serum phosphate levels have been observed with MLN2480 administration. While a decrease in phosphate level alone (asymptomatic) is not necessarily clinically meaningful, it is important to rule out an accompanying clinical condition. See the recommendations in Table 6.14.

Table 6.14 Management of Hypophosphatemia

Participation Time Point	Recommendation
Screening Period	• Evaluate baseline nutritional status. Initiate daily dietary supplementation from such staples as dairy products and beans as indicated. • Initiate empiric phosphate supplementation of 250 mg-1000 mg daily dose of PO_4 should risk of hypophosphatemia be suspected. Amount of PO_4 supplementation is per investigator discretion. • Evaluate serum phosphate before and >48-72 hours after initiating daily dietary and PO_4 supplementation. • If hypophosphatemia ≥Grade 1 prior to Cycle 1 Day 1 despite above guidelines, evaluate urine phosphate to rule out urinary excretion.
Prior to start of study treatment	• Maximize phosphate supplementation targeting up to 1000 mg of PO_4/day as tolerated and /or consider adding vitamin D2 ergocalciferol of 1.25 mg (50,000 U) QW • In subjects with excess urine phosphate, consult an endocrinologist and/or nephrologist to ensure appropriate management and further evaluation before and during study treatment
In patients with decreasing serum phosphate while on study treatment	• Evaluation: Check urine phosphate and consult with an endocrinologist and/or a nephrologist if urine phosphate levels are elevated • Increase phosphate supplements up to 1000 mg QD if tolerable • For patients on maximal phosphate supplements and or intolerance to supplementation, add vitamin D2 ergocalciferol 1.25 mg (50,000 U) QD plus calcium in patients with hypocalcemia of any grade.

Abbreviations: PO_4=phosphate, QD=each day, QW=each week.

6.8.1.4 Rash

Rashes (maculopapular, dermatitis acneiform, and pruritus) have been observed with MLN2480, MLN0128, and cetuximab administration. Patients should avoid excess exposure to sunlight and use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with an SPF > 15. Should a rash occur, the recommendations in Table 6.15 should be followed. NOTE: Should a Grade 2 or 3 rash occur, photographic documentation is recommended.

Table 6.15 Management of Rash

AE Severity	Event Definition	Recommendation
Grade 1	Macular or papular eruption or erythema without associated symptoms	• Cold compresses • Oral antihistamines • Initiate use of topical steroids (ie, hydrocortisone cream 1%-2.5% or triamcinolone cream 0.1)
Grade 2	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 30% of body surface area (BSA)	• Follow at least weekly • Assess with bacterial and fungal cultures and treated with systemic agents as appropriate (Level of Evidence II). Initiate treatment with minocycline 100 mg BID with or without topical clindamycin BID until Grade 1 or resolved • Consider MLN2480 dose reduction to next lowest dose after discussion between the investigator and sponsor
Grade 3 or higher	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥ 30% BSA. Generalized exfoliative, ulcerative, or bullous dermatitis.	• A dermatologist should be consulted, a biopsy could be considered for rash characterization • Initiate treatment with minocycline 100 mg BID with or without topical clindamycin BID until Grade 1 or resolved • Dose reduce to next lowest dose or hold administration of MLN2480 until resolved to Grade 1 or baseline

Source: Guidelines for Rash/Dermatitis adapted from Lemech and Arkenau, 2012.[47]
Abbreviations: BID = twice daily; BSA = body surface area.

6.8.1.5 Cardiac Events

Cardiac events, including heart failure and atrial fibrillation, have been observed with MLN2480 administration. Should a cardiac event occur, follow the recommendations in Table 6.16.

Table 6.16 Management of Cardiac Events

Event Definition	Recommendation
• Asymptomatic, absolute decrease in LVEF of 10%-20% from baseline.	• Do not modify the dose of MLN2480.
• Symptomatic congestive heart failure • Asymptomatic absolute decrease in LVEF of greater than 20% from baseline.	• Withhold MLN2480 for up to 4 weeks, if improved to grade 1 or baseline, then resume at 140 mg (QD) or to the next lower dose level (QW).

6.8.2 MLN0128

6.8.2.1 Management of Hyperglycemia

Hyperglycemia and hyperinsulinemia are known toxicities associated with inhibition of mTOR and related pathways based on nonclinical studies. A rise in fasting plasma glucose has been observed as early as 1 to 2 days following oral administration of MLN0128.

In addition to obtaining fasting blood glucose levels at the clinic visits outlined in the Schedules of Events for Arm 1, all patients receiving MLN0128 will be provided with a glucometer and trained in its use to monitor their daily predose fasting blood glucose (FBG) levels at home during Cycles 1 and 2; see Section 7.4.16.2. Guidelines for management of hyperglycemia in patients receiving MLN0128 are presented in Table 6.17.

Table 6.17 Management of MLN0128-Associated Hyperglycemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	Fasting blood glucose > ULN–160 mg/dL	Continue close monitoring of blood glucose. Initiate oral hypoglycemic agent.	None
2	Fasting blood glucose > 160–250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥ 3	Fasting blood glucose > 250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤ Grade 2. Resume MLN0128 based on timing of recovery: • ≤ 1 week: resume at same dose and schedule • > 1 but ≤ 2 weeks: reduce by 20% • 2 weeks: stop MLN0128 and discontinue patient from the study

Prevention/Prophylaxis

- Follow fasting glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Recommend lifestyle modifications, as appropriate (balanced diet including limited consumption of carbohydrates and alcohol, increased physical activity). Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy is recommended to prevent higher grade hyperglycemia.
- FBG levels ≥ 150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.

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

Based on the clinical experience in MLN0128 trials, most episodes of hyperglycemia observed have been Grade 1 or Grade 2 and have responded quickly to oral metformin. Hyperglycemia has not been dose limiting in these trials since the institution of a standard regimen for the early treatment of hyperglycemia. Glucose levels in patients who develop hyperglycemia during this study should be closely monitored. The investigator may choose either to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting glucose > ULN ≤ 160 mg/dL) or consider initiating treatment with an oral hypoglycemic agent such as metformin. All patients with ≥ Grade 2 hyperglycemia (fasting glucose > 160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated while continuing on MLN0128 treatment. The investigator should consult an endocrinologist if needed to aid in optimizing the hyperglycemia treatment plan of the patient.

It is recommended that patients be treated initially with a fast-acting insulin sensitizer, such as oral metformin (500 mg QD), and titrate up to a maximum of 1000 mg orally BID as needed. Concurrent addition to metformin of dipeptidyl peptidase-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution due to the higher risk of inducing hypoglycemia in patients. The dose of oral hypoglycemic agents should be adjusted in patients with renal insufficiency.

6.8.2.2 Management of Hyperlipidemia

Guidance on MLN0128 dose modification for hyperlipidemia in patients receiving MLN0128 is provided in Table 6.18.

Table 6.18 Management of MLN0128-Associated Hyperlipidemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	Cholesterol: > ULN - 300 mg/dL Triglycerides: > 150-300 mg/dL	None	None
2	Cholesterol: > 300-400 mg/dL Triglycerides: > 300-500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥ 500 mg/dL should be treated urgently due to risk of pancreatitis.	Maintain MLN0128 dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Cholesterol: > 400-500 mg/dL Triglycerides: > 500-1000 mg/dL	Same as for Grade 2	Hold MLN0128 dose until recovery to ≤ Grade 1, then restart with a 20% dose reduction.
4	Cholesterol: > 500 mg/dL Triglycerides: > 1000 mg/dL	Same as for Grade 2	Discontinue treatment.

Prevention/Prophylaxis

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

Abbreviation: ULN = upper limit of the normal range.

6.8.2.3 Management of Oral Mucositis

Guidance for the management of oral mucositis in patients receiving MLN0128 is provided in Table 6.19.

Table 6.19 Management of MLN0128-Associated Oral Mucositis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic or mild symptoms	Nonalcoholic mouthwash or 0.9% salt water rinse; consider topical corticosteroids at earliest signs of mucositis.	None
2	Moderate pain not interfering with oral intake; modified diet indicated	Topical analgesic mouth treatments; topical corticosteroids; initiate antiviral or antifungal therapy if indicated.	Maintain MLN0128 dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Severe pain interfering with oral intake	Same as for Grade 2; consider intralesional corticosteroids.	Hold dose until recovery to ≤ Grade 1, then restart with a 20% dose reduction.
4	Life-threatening consequences	Same as for Grade 2; consider intralesional corticosteroids.	Discontinue MLN0128 treatment.

Prevention/Prophylaxis

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

6.8.2.4 Management of Nausea and/or Vomiting

Guidance for the management of nausea and/or vomiting in patients receiving MLN0128 is provided in Table 6.20.

Table 6.20 Management of MLN0128-Associated Nausea and/or Vomiting

Grade	Description	Treatment	MLN0128 Dose Modification
≤ 2	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours	Maximize antiemetic therapy; consider IV fluid hydration.	None
≥ 3	Inadequate oral intake; ≥ 6 episodes of vomiting within 24 hours	Maximize antiemetic therapy; initiate tube feeding, IV fluids, or TPN.	Hold until ≤ Grade 1; resume MLN0128 without dose modification
Prevention/Prophylaxis Prophylactic use of antiemetic, antinausea, and antidiarrheal medications is encouraged; these may be administered before each dose of MLN0128 as needed throughout the study. Due to risk of QTc prolongation, ondansetron may not be used.			

Abbreviations: IV = intravenous; TPN = total parenteral nutrition.

6.8.3 Alisertib

6.8.3.1 Management of Nausea and Vomiting

Prophylactic antiemetic therapy may be used in patients receiving alisertib per standard of care. Because of the potential for benzodiazepines to cause sedation, the use of benzodiazepines for antiemetic prophylaxis should be reserved for patients who cannot be satisfactorily managed otherwise.

6.8.3.2 Management of Diarrhea

Antidiarrheal medications will not be used prophylactically; however, patients should be instructed to take loperamide or comparable antidiarrheal medication per standard guidelines. Fluid intake should be maintained to avoid dehydration.

6.8.3.3 Management of 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; the alisertib dose should be reduced whenever indicated.

6.8.4 Paclitaxel

Please refer to the paclitaxel USPI [9] or SmPC [10] for more information on the management of clinical events in patients receiving paclitaxel.

6.8.5 Cetuximab

Please refer to the cetuximab SmPC [11] for more information on the management of clinical events in patients receiving cetuximab.

6.8.6 Irinotecan

Please refer to the irinotecan SmPC [12] for more information on the management of clinical events in patients receiving irinotecan.

6.9 Blinding and Unblinding

This is an open-label study; no blinding methods will be utilized.

6.10 Description of Investigational Agents

Upon receipt of drug supply, contents must be verified promptly and the proper contacts notified of any discrepancies or damages as described in the Study Manual.

6.10.1 MLN2480

MLN2480 may be provided to investigator sites with 2 slightly different formulations. Initially, sites will be supplied study drug with the formulations as described below:

The initial drug product consists of MLN2480 active substance and other commonly used, compendial excipients that include microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, vinylpyrrolidone-vinyl acetate copolymer (copovidone), and sodium croscarmellose.

In the summer of 2015, MLN2480 will be provided in an optimized formulation as described below:

The optimized drug product consists of MLN2480 active substance and other commonly used, compendial excipients that include microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, vinylpyrrolidone-vinyl acetate copolymer (copovidone), sodium croscarmellose and Opadry®.

The availability of the optimized drug product to investigator sites will be dependent on country regulatory approvals. Until appropriate approvals are in place for the optimized drug product, the investigator will only receive the initial drug product.

The MLN2480 drug product is formulated as an immediate-release tablet for oral administration. The 3 dosage strengths (initial and optimized formulations) and the color of their bottle label are described as follows. The global booklet labels have a colored cover page.

- 20 mg: white-to-off-white round tablet. Initial: light blue
- 20 mg: red round tablet. Optimized: light blue
- 70 mg: yellow oblong tablet. Optimized: yellow
- 100 mg: white-to-off-white oval tablet. Initial: white
- 100 mg: red-to-yellowish-red oval tablet. Optimized: white

The drug product is labeled MLN2480. MLN2480 tablets, 20 mg, 70 mg, and 100 mg, are packaged with desiccant and cotton in 40 cc white wide mouth round high density polyethylene bottles equipped with 33 mm polypropylene child-resistant caps and induction sealed.

There are 15 tablets in each bottle for the initial formulation study. With the optimized material, the number of tablets per bottle will increase to 16 in each bottle for the 20 mg, 70 mg, and 100 mg dosage strengths.

Each bottle of MLN2480 study medication will be labeled with a multi-panel booklet label containing pertinent study information and a regulatory caution statement. The study drug is labeled to be used across protocols within the MLN2480 program. Therefore, the bottle booklet label will identify the study number as "C2800_". The last digit should be written in based on the identified protocol number noted on the Packing List. In addition, if the investigational pharmacy is participating in multiple MLN2480 studies, it is mandatory that the study drug is segregated based on the protocol number.

6.10.2 MLN0128

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

strengths are formulated into size-2 capsules. Each strength is differentiated by color, as listed below:

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

MLN0128 is provided in 60-cc high-density polypropylene bottles with polypropylene, child-resistant caps and is induction sealed. Please refer to the MLN0128 IB for additional information.

6.10.3 Alisertib

Alisertib drug product is supplied as the enteric-coated tablet dosage form, with dose strength expressed as the milligrams of active drug (10-mg alisertib, free acid). The key formulation excipients of the alisertib tablet formulation that aid in the in vivo absorption of the drug are the buffer (sodium bicarbonate), the surfactant (sodium lauryl sulfate), the disintegrant (croscarmellose sodium), and the enteric coating. Refer to the alisertib IB for full details.

6.10.4 Paclitaxel

Paclitaxel is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the Pharmacy Manual. Please refer to the paclitaxel USPI [9] or SmPC [10] for more information regarding paclitaxel.

6.10.5 Cetuximab

Cetuximab is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the Pharmacy Manual. Please refer to the cetuximab SmPC [11] for more information regarding cetuximab.

6.10.6 Irinotecan

Irinotecan is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the Pharmacy Manual. Please refer to the irinotecan SmPC [12] for more information regarding irinotecan.

6.11 Preparation, Reconstitution, and Dispensation

Each of the combination partners used in this study is an anticancer drug; as with other potentially toxic compounds, caution should be exercised when handling these agents. In case of contact with broken capsules or tablets, raising dust should be avoided during the clean-up operation.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the bottles or drug, it should not be used. The packaging or bottle in question should be saved at the study site and the problem immediately reported to Millennium. Contact information is supplied in the Pharmacy Manual.

Study drug products may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with powder (eg, from a broken capsule or 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.

6.11.1 Dispensation of Oral Agents (MLN2480, MLN0128, and Alisertib)

The individual preparing the study drugs should first review dispensing instructions provided in the Pharmacy Manual. The pharmacist or medically qualified staff will dispense MLN2480 tablets, MLN0128 capsules, and alisertib tablets to enrolled patients per their respective treatment arm assignment. Patients will be given clear dosing instructions from the investigator for home storage and administration use, including the requirement that the study drugs must be stored in their original containers and that tablets/capsules are to be swallowed whole and not chewed or manipulated in any way.

Patients will also receive diary cards to record dosing compliance of their study drug assignment, with instructions for their completion.

6.11.2 Paclitaxel

Please refer to the paclitaxel product label for instructions and precautions regarding preparation, storage, dispensation, and accountability.

6.11.3 Cetuximab

Please refer to the cetuximab product label for instructions and precautions regarding preparation, storage, dispensation, and accountability.

6.11.4 Irinotecan

Please refer to the irinotecan product label for instructions and precautions regarding preparation, storage, dispensation, and accountability.

6.12 Packaging and Labeling

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 Pharmacy Manual. The labels for drug products provided by Millennium will include conditions for storage, lot number, and other pertinent information such as batch/lot number, and caution statement, and will comply with local country requirements as appropriate. Drug products should not be used after the stated expiration or retest date; see the Pharmacy Manual for details.

6.13 Storage, Handling, and Accountability

Each of the study drugs used in this trial are anticancer agents and should be handled with due care; see Section 6.11. Upon receipt at the investigative site, study drug products must be stored at temperatures as described in the Pharmacy Manual or relevant documentation in their original packaging and protected from light and excessive humidity in a monitored, locked, secure area with limited access. Storage area temperature conditions must be monitored and recorded daily. All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. Study site staff must instruct patients on how to store and administer oral study drug agents that are dispensed for at-home administration.

Accountability for study drug product is the responsibility of the investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (patient-by-patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. A written explanation must be provided for any discrepancies. Patients are to be instructed on proper accountability of the take-home study drugs and will be instructed to return any unused drug in the original packaging along with their completed diary cards at the appropriate clinic visits and as described in the Study Manual. The investigator must destroy or return all unused drug product provided by

Millennium; refer to the Pharmacy Manual for more information and for complete information regarding storage, handling, accountability, and drug-destruction policies. Please also refer to the most recent paclitaxel product label for further information regarding the proper storage and handling of paclitaxel.

7. STUDY CONDUCT

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

7.1 Study Personnel and Organizations

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

7.1.1 Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before patients are screened at each study site, the CRO will review study responsibilities with the investigators and other study site staff, as appropriate.

7.1.2 Remote Data Capture

Patient information will be captured and managed by study sites on eCRFs by a remote data capture system (RAVE).

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

Neither randomization nor stratification is planned for this open-label study. Patients will be assigned to a treatment group based on diagnosis, clinical judgment, and treatment arm availability.

7.4 Study Procedures

A detailed visit-by-visit schedule of study procedures is provided in the respective Schedules of Events for each treatment arm.

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, and End of Study. Evaluations during the Screening period are to be conducted within 28 days before the first dose of any study drug on Cycle 1, Day 1. All End of Study evaluations should occur 30 (+ 10) days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

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

7.4.1 Informed Consent

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

7.4.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening (within 28 days before the first dose of any study drug on Cycle 1, Day 1).

7.4.3 Patient Demographics

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

7.4.4 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy, including prior treatment and recurrences. In addition, concomitant medications will be recorded as specified in Section 7.4.14. All AEs that occur during the Screening period

(following informed consent, but prior to study drug administration) will be recorded as part of the patient's medical history.

7.4.5 Physical Examination

A physical examination will be completed per standard of care at the times specified in the appropriate Schedules of Events. Any clinically relevant findings will be documented.

7.4.6 Patient Height and Weight

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

7.4.7 Dermatological Examinations and Photographs

All patients in Arms 1 through 5 will be assessed by the investigator or a consulting dermatologist for skin lesions, especially for nevi, keratoacanthomas, hair discoloration, and squamous cell carcinomas at the times specified in the appropriate Schedules of Events. The examinations will include the entire skin. The screening examination may include digital dermatological photographs to document each patient's baseline skin before treatment, including any pretreatment skin lesions. Any new or changing skin lesions noted during the course of treatment will be documented with new digital photographs, and new lesions that develop during treatment should also be recorded on the AE form. Treatment-emergent lesions that are suspected keratoacanthomas or squamous cell carcinomas will be biopsied and adequately treated; other lesions may be biopsied and treated per the discretion of the investigator/dermatologist. Refer to the Study Manual for further details.

7.4.8 Vital Signs

Vital sign measurements include diastolic and systolic blood pressure, heart rate, and oral temperature.

7.4.9 Echocardiogram or Multiple Gated Acquisition Scan

An ECHO or MUGA scan will be administered at the time points specified in the relevant Schedules of Events, or as clinically indicated.

7.4.10 Enrollment

A patient is considered to be enrolled in the study after receiving 1 dose of study drug on Cycle 1, Day 1. Procedures for completion of the enrollment information are described in the Study Manual.

7.4.11 Patient Dosing Diary

The patient diary is used as a source document for patient dosing compliance and is completed by all patients throughout the Treatment period. Thorough instructions regarding the use of the patient dosing diary, regarding diary review and return of study drug containers and/or unused study drug, will be provided before dosing on Cycle 1, Day 1 and at any other time during the study per the site discretion. Patients should be encouraged to bring their diary and their study drug container(s) to each scheduled clinic visit. Study staff will review all diary entries with the patients at least once weekly (or at each visit if they occur more than 1 week apart) and will check the patient diary versus the patient's supply of remaining study drug to ensure dosing compliance. Understanding of and compliance with the dosing and diary instructions should be continually evaluated and addressed as needed throughout trial participation.

7.4.12 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status (see Section 14.1) will be assessed at the times specified in the relevant Schedules of Events.

7.4.13 Electrocardiogram

A single 12-lead ECG will be administered at the time points specified in the relevant Schedules of Events and as clinically indicated. Electrocardiogram assessments are to be performed after the measurement of vital signs, with the patient supine and rested for 5 minutes, and before any closely timed blood collection. The dates and exact times of ECG recordings will be recorded. Any findings from ECGs collected after initiation of study treatment will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline. Although the number of scheduled ECG measurements will not be increased, the timing may be changed if emerging data indicate that an alteration in the ECG schedule is needed.

7.4.14 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first. Medications and therapies that are prohibited for each treatment combination are summarized in Section 6.5. Medications or procedures that are permitted in specific treatment arms are described in Section 6.6. See Section 6.7 for additional precautions and restrictions.

7.4.15 Adverse Events

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

7.4.16 Clinical Laboratory Evaluations

Blood samples for analysis of hematology and clinical chemistry parameters, and urine for urinalysis will be obtained as specified in the relevant Schedules of Events. Clinical laboratory evaluations will be performed as outlined in the following.

Clinical laboratory evaluations for study endpoints will be performed centrally. Handling and shipment of the relevant clinical laboratory samples will be outlined in the Study Manual. Clinical laboratory evaluations for safety will be performed locally. Decisions regarding study eligibility and safety throughout the study may be made using local laboratory results.

Clinical Chemistry, Hematology, Coagulation, and Urinalysis

Blood samples for analysis of the following clinical chemistry, coagulation, hematological parameters, and urine samples for urinalysis will be obtained at the time points specified in the relevant Schedules of Events. See Section 7.4.19.1 for minimum coagulation requirements needed before performing invasive procedures such as tumor biopsies.

Hematology and Coagulation

- Hemoglobin
- Hematocrit
- Platelet (count)
- Red blood cells
- White blood cells
- Absolute reticulocyte count (*only for patients who experience recurrent anemia with hemoglobin < 9 g/dL despite blood transfusion*)
- Absolute differential
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])
- Activated partial thromboplastin time (aPTT)
- Prothrombin time/international normalized ratio (PT/INR)
- Urine phosphate (as clinically indicated)
- Vitamin D (as clinically indicated)

Serum Chemistry

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

Urinalysis

- Turbidity and color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Blood
- Nitrite or leukocyte esterase
- Glucose

7.4.16.1 Hematology and Serum Chemistry Requirements During the Treatment Period

If at any time a patient develops an ANC < 500/μL or a platelet count < 25,000/μL, blood samples must be collected every 2 to 3 days and study treatment withheld until ANC returns to > 1000/μL and platelet counts return to > 50,000/μL.

Hematology results and serum chemistry results will be evaluated before each patient is allowed to start a given treatment cycle. For a patient to begin a new cycle, the following criteria must be met:

- ANC must be ≥ 1500/mm^3
- Platelet count must be ≥ 75,000/mm^3 (≥ 100,000/mm^3 for patients receiving paclitaxel)
- Any toxicity considered by the investigator to be related to study therapy must have resolved to baseline or have not worsened by > 1 Grade over baseline, and must be considered acceptable by the physician (eg, hemoglobin level manageable by transfusion or growth factors)

7.4.16.2 For Patients Receiving MLN0128

7.4.16.2.1 New York Heart Association Classification of Cardiac Disease

The NYHA classification of cardiac disease (see Section 14.2) will be assessed and recorded at the times specified in the relevant Schedules of Events.

7.4.16.2.2 Glucose and Lipid Laboratory Evaluations

HbA1c

Glycosylated hemoglobin (HbA1c) will be measured in patients receiving MLN2480 + MLN0128 at the time points indicated in the relevant Schedules of Events.

Fasting Glucose Measurements

Fasting glucose will be measured in the clinic at the time points specified in the relevant Schedules of Events before study drug administration. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) before each of these measurements.

In addition to obtaining fasting glucose levels at the clinic visits as outlined in the Schedules of Events, all patients will be given a glucometer to monitor their daily predose fasting blood glucose levels at home throughout Cycle 1 and Cycle 2:

- The patient will be provided an in-home glucometer on Cycle 1, Day 1. Patients will be trained on proper use of the glucometer and instructed to collect a daily predose

fasting glucose level every morning at home after fasting overnight (NPO except water and/or medications after midnight or for a minimum of 8 hours) for each measurement. The patient will be instructed to contact the site immediately if the value is abnormal (ie, ≥ 150 mg/dL, based on local ULN) to receive further instructions on the management of their hyperglycemia.

- Patients will be instructed to bring the glucometer with them to each study visit so that the data can be reviewed. Investigators are responsible for reviewing the home glucose monitoring logs for hyperglycemia.

- Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Any clinically significant findings should be reported as AEs as appropriate.

See Section 6.8.2.1 for details on the management of hyperglycemia in patients receiving MLN0128.

If no irregularities in the fasting blood glucose level are observed during Cycles 1 and 2, in-home daily fasting glucose testing will be discontinued beginning with Cycle 3. However, fasting glucose levels will continue to be tested at the clinic visits as specified on the Schedules of Events, and at other times as clinically indicated per standard of care.

Fasting Lipid Profile

Prospective monitoring for hyperlipidemia in patient receiving MLN0128 will be managed through fasting lipid testing at the time points specified in the relevant Schedules of Events, and as clinically indicated. The fasting lipid profile for patients receiving MLN0128 includes the following:

- Total cholesterol
- Triglycerides
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)

7.4.17 Pregnancy Tests

A serum pregnancy test will be performed for women of childbearing potential at screening and within 72 hours before the first dose of study drug, and according to the relevant Schedules of Events table. Test results must be available and negative before the first dose

of study drug is administered. If Cycle 1, Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations. If a female patient or a male patient's partner becomes pregnant or suspects pregnancy while participating in this study, the investigator must be informed immediately (see Section 9.2).

7.4.18 Pharmacokinetic Measurements

7.4.18.1 Escalation Phase

- Arm 1: Blood samples for the measurement of plasma concentrations of MLN2480 and MLN0128 will be collected in Cycle 1 at the time points listed in Table 1.2.
- Arm 2: Blood samples for the measurement of plasma concentrations of MLN2480 and alisertib will be collected at the time points listed in Table 1.5.
- Arm 3: Blood samples for the measurement of plasma concentrations of MLN2480 and paclitaxel will be collected at the time points listed in Table 1.8 and Table 1.9.
- Arm 4: Blood samples for the measurement of plasma concentrations of MLN2480 and cetuximab will be collected at the time points listed in Table 1.12.
- Arm 5: Blood samples for the measurement of plasma concentrations of MLN2480 and irinotecan will be collected at the time points listed in Table 1.15.
- All Arms: In addition to the scheduled PK sample collections, a blood sample to measure plasma concentrations of MLN2480 and/or combination agents should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged by the investigator to be related to treatment, irrespective of the cycle or day of the AE occurrence. The date and exact time of the unscheduled sample collection should be recorded, along with the date and exact time of the most recent dose administration before the unscheduled sample collection.

7.4.18.2 Expansion Phase

The PK sampling schedules for the Expansion phase, if applicable, are shown in Table 1.9, Table 1.12, and Table 1.15.

7.4.19 CCI

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7.4.19.1 Coagulation Levels Required Before Biopsies

Within 48 hours before any tumor biopsy or other invasive procedure (bone marrow biopsy, etc), patients must meet the following criteria: platelet count > 75,000/mm^3 and an aPTT and PT within the normal range; must not have an ECOG performance status > 1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure.

7.4.20 Disease Assessment

Patients will undergo a CT scan with contrast as appropriate, or MRI, X-ray, and/or bone scanning to monitor and assess disease progression using RECIST criteria (version 1.1).[46]

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. Objective assessments (per the investigator) will be performed at each time point as described in the relevant Schedules of Events table. When possible, the same qualified physician will interpret results to reduce variability.

7.5 Completion of Study

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

7.6 Withdrawal of Patients From Study

Patients will be informed that they have the right to discontinue study treatment at any time for any reason, without prejudice to their medical care.

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

- Adverse event
- Protocol violation
- Progressive disease
- Symptomatic deterioration
- Unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Completed maximum number of cycles
- Other

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

7.7 Replacement of Patients

During the Escalation stage, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced. During the Escalation stage, patients who do not complete at least 75% of their doses in Cycle 1 will also be replaced.

7.8 Study Compliance

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

7.9 Study Stopping Rules

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, excessively frequent, or unacceptable risk to the patients enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product.

Millennium Pharmaceuticals, Inc. (Millennium) may terminate this study at any time, after informing investigators. Investigators will be notified by Millennium if the study is placed on hold, completed, or closed.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

8.1.1 Determination of Sample Size

Overall, the total study sample size will be approximately 125 patients.

Escalation phase: Approximately 49 evaluable patients with advanced solid tumors (approximately 4 for Arm 1, approximately 15 for Arm 2, approximately 18 for Arm 3; approximately 6 for Arm 4; approximately 6 for Arm 5) will be enrolled. Because a 3 + 3 dose escalation design will be used, the actual sample size will depend upon the number of dose escalation steps and number of patients required per cohort.

Expansion: Approximately76 evaluable patients with advanced solid tumors (approximately 16 for Arm 3 (QW dosing schedule) and approximately 30 each for Arms 4 and 5) will be enrolled to further evaluate the safety and preliminary antitumor activity of the combination regimens selected during Escalation.

8.1.2 Randomization and Stratification

Neither randomization nor stratification is planned for this study. Patients will be assigned to treatment arm by the investigator according to instructions from the sponsor.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: patients who receive at least 1 dose of study drug on Cycle 1, Day 1 will be used for all safety and PFS analyses.

- PK-evaluable population: patients with sufficient dosing data and concentration-time data of MLN2480 and the respective combination agent to permit calculation of PK parameters.

- Response-evaluable population: patients who receive at least 1 dose of study drug, have measurable disease at baseline, and 1 postbaseline response assessment will be used for response-related efficacy analyses (ORR, DOR, time to response, and PFS).

- DLT-evaluable population: patients who either experience DLT during Cycle 1, or receive ≥ 75% of scheduled doses and complete all study procedures in Cycle 1 without DLT.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed with the exception of AUC calculation in PK analyses where the predose concentration in an individual following multiple-dose administration may be used in place of the concentration at the end of the dosing interval (or vice versa) if 1 of these data points is not available and scientific considerations based on PK characteristics of MLN2480 and the respective combination agent support conclusion of achievement of steady-state on the day of PK sampling.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose level and treatment arm. Data to be evaluated will include at least age, sex, race, weight, and height. Components of disease severity assessment in addition to relevant patient and disease assessments and laboratory parameters will be presented, if appropriate.

8.1.6 Efficacy Analysis

Analysis of efficacy measures will be descriptive. Antitumor activity of the combination arms will be based on the best overall response. Investigators will assess response per RECIST guidelines (version 1.1)[46] at each scheduled time point. The best overall response for each patient will be programmatically derived from among the reported responses.

Efficacy parameters include ORR (complete response + partial response), time to response, DOR, and PFS. The response rates, time to response, and DOR will be analyzed based on the response-evaluable population. PFS will be analyzed based on safety population.

- Time to response is defined as the time from the patient's date of enrollment to the date of the first documentation of a confirmed response.
- Duration of response is defined as the time from the date of first documentation of a confirmed response to the date of first documented progression of disease.
- PFS is defined as the time from the date of enrollment to the date of first documented progression of disease or death.

Duration of response and PFS will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates. If appropriate, the association between responses and PFS among patients with or without responses may be examined.

Response categories, DOR, time to response, and PFS will be presented in listings and summarized, if appropriate. The changes of target lesion measurements from baseline will be presented in listings and graphically, if appropriate.

8.1.7 Pharmacokinetics/Biomarkers

Pharmacokinetic Analysis

Individual and mean plasma concentration data will be plotted over time. Descriptive statistics will be presented for MLN2480, MLN0128, and alisertib plasma PK parameters (including but not limited to C_{max}, T_{max}, and $AUC_{0\text{-}tau}$). Descriptive statistics will be presented for paclitaxel, cetuximab, and irinotecan plasma PK parameters (including but not limited to C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $t_{1/2}$, clearance, and volume of distribution).

The relationships between dose and C_{max} and AUC may be explored graphically for dose proportionality.

Biomarkers

CCI

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8.1.8 Safety Analysis

The incidence of DLT will be tabulated for each combination arm and in each phase of the study. The DLT-evaluable population will be used for the analysis of DLT. In addition, to assess the relationship between toxicities and the tested dose regimens of the combination arms, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group and treatment arm.

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

Treatment-emergent AEs that occur after administration of the first dose of study drug and through approximately 30 days after the last dose of study drug will be tabulated. If other antineoplastic therapy is initiated before this time point, AEs that occur subsequent to the initiation of that therapy will not be captured.

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

- Treatment-emergent AEs (TEAEs)
- Combination study drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher combination study drug-related TEAEs
- The most commonly reported TEAEs
- SAEs and combination study drug-related SAEs
- TEAEs resulting in study drug discontinuation
- TEAEs resulting in study drug reduction

A listing of on-study deaths will be provided. Tabulation also will be provided that enumerates AEs by maximum CTCAE grade intensity.

Exposure to the study drugs will be listed and summarized for each investigational agent and will include the total doses received, number of treatment cycles, number of doses, and relative dose intensity of each study drug.

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

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs weight, and ECOG scores over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. These tables will summarize the number of patients with each baseline NCI CTCAE grade and changes to the worst NCI CTCAE grade during study.

All concomitant medications and procedures collected from screening through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy (whichever comes first) will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of each combination arm.

Electrocardiogram Analysis

Electrocardiogram parameters will include PR, RR, QT, QTc (QTcB [Bazett]) and QTcF), QRS, and heart rate.

The ECG intervals (QT, QT adjusted by an appropriate correction [QTcB and QTcF], PR, QRS, and RR) and heart rate will be listed and summarized at each scheduled time point, along with mean change from baseline to each posttreatment time point. A summary or listing of ECG abnormalities will be presented.

8.1.9 Interim Analysis

No formal interim analysis will be performed. Safety and available PK data will be reviewed jointly by Millennium and investigators on an ongoing basis for the purposes of safety monitoring and dose escalation decisions.

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

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

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

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

SAE Reporting Contact Information

CCI [redacted]

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and ethics committees as applicable, in accordance with national regulations in the countries where the study is conducted. Specifically in the EU, the sponsor will ensure that all relevant information from SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the regulatory authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than 7 days after knowledge by the sponsor of such a case, and relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the regulatory authorities concerned and to the Ethics Committee concerned as soon as possible within a maximum of 15 days of first knowledge by the sponsor. The sponsor will also inform all the investigators in the clinical trial.

Once a year throughout the conduct of the clinical trial, the sponsor will provide the regulatory authorities in whose territory the clinical trial is being conducted and the Ethics Committees with a listing of all SUSARs that have occurred over the past year and a report of the subjects' safety.

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was administered on Cycle 1, Day 1 are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[45] The criteria are provided in the Study Manual.

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

9.3 Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy (whichever occurs first), and recorded in the eCRFs. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee and recorded in the Safety database from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the eCRF. Pretreatment AEs (nonserious) will be recorded in the eCRF as part of the patient's medical history. If a pretreatment event worsens following initiation of study drug, the corresponding TEAE is documented in the clinical database.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the signing of the informed consent form through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to

the Millennium Department of Pharmacovigilance or designee (see Section 9.2). The pregnancy must be followed for the final pregnancy outcome.

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

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

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

10. ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

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

10.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated,

web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

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

10.3 Electronic Case Report Form Completion

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

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

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

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

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (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 MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

PPD

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

10.12 Closure of the Study

The sponsor will notify the competent Health Authorities and the IECs/IRBs regarding study closure and the results of the clinical trial, as required.

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

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

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

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

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

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 MLN2480, MLN0128, 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 MLN2480, MLN0128, and alisertib and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

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

12. INVESTIGATOR AGREEMENT

I have read Protocol C28002 Amendment 6: A Multiarm, Open-label, Phase 1b Study of MLN2480 (an Oral A-, B-, and CRAF Inhibitor) in Combination With MLN0128 (an Oral mTORC 1/2 Inhibitor), or Alisertib (an Oral Aurora A Kinase Inhibitor), or Paclitaxel, or Cetuximab, or Irinotecan in Adult Patients With Advanced Nonhematologic Malignancies.

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

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

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

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14. APPENDICES

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

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

Source: Oken MM, et al. 1982.[48]

14.2 New York Heart Association Classification of Cardiac Disease

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 1994.[49]

14.3 Cockcroft-Gault Equation

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

OR

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

Source: Cockcroft DW and Gault MH. 1976.[50]

14.4 List of Relevant Cytochrome P450 Inhibitors and Clinically Significant Enzyme Inducers

Strong CYP2C19 Inhibitors	**Strong CYP2C8 Inhibitors**	
fluconazole	gemfibrozil	
fluvoxamine		
ticlopidine		
Moderate CYP3A4 Inhibitors		
amprenavir	darunavir/ritonavir	fosamprenavir
aprepitant	diltiazem	grapefruit juice[a]
atazanavir	erythromycin	imatinib
ciprofloxacin	fluconazole	verapamil
Strong CYP3A4 Inhibitors		
boceprevir	ketoconazole	ritonavir
clarithromycin	lopinavir/ritonavir	saquinavir
conivaptan	mibefradil[b]	telaprevir
grapefruit juice1	nefazodone	telithromycin
indinavir	nelfinavir	voriconazole
itraconazole	posaconazole	
Clinically Significant Enzyme Inducers		
carbamazepine	rifampin	
phenobarbital	rifapentine	
phenytoin	St. Johns Wort	
rifabutin		

Note that these lists are not exhaustive.

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

a The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a strong CYP3A inhibitor when a certain preparation was used (eg, high dose, double strength) or as a moderate CYP3A inhibitor when another preparation was used (eg, low dose, single strength).

b Withdrawn from the United States market because of safety reasons.

14.5 Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 6 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Add a cohort of patients with NSCLC and non-V600 BRAF mutations.

The primary change occurs in Section 4.1 Overview of Study Design:

Added text: Once the maximum tolerated dose (MTD) for each combination treatment arm has been established in the Escalation phase, up to 3 combination treatment arms and one monotherapy will be evaluated in the Expansion phase based on tolerability and exposure data collected during Escalation. The combination of MLN2480 + paclitaxel will be administered to patients with KRAS exon 2 or BRAF non-V600 mutation-positive NSCLC who are naïve to previous treatment with RAF or MEK inhibitors. The combination of MLN2480 + cetuximab will be administered to patients with BRAF V600 or non-canonical RAS mutation-positive mCRC. The combination of MLN2480 + irinotecan will be administered to patients with previously treated mCRC who are naïve to previous treatment with RAF or MEK inhibitors. **Finally, MLN2480 will be administered QOD to patients with NSCLC with non-V600 BRAF mutations.**

Rationale for Change:

To define the patient population for enrollment in the Arm 6 expansion cohort of MLN2480 given as monotherapy QOD in patients with NSCLC and non-V600 BRAF mutations. This is a population that does not respond to currently available V600 BRAF inhibitors and so remains underserved.

The following sections also contain this change:

- Protocol Summary.
- Study Overview Diagram.
- New Schedules of Events for Arm 6.
- Section 1.1.1 Disease Under Study.
- Section 1.3.1 MLN2480.
- New Section 1.4.6 MLN2480 Monotherapy Every Other Day (Arm 6).
- New Section 1.5.1.6 MLN2480 QOD Monotherapy (Arm 6).
- Section 4.2 Number of Patients.
- Section 6.1.1 MLN2480 Administration (All Arms).
- New Section 6.1.7 MLN2480 in Non-V600 BRAF NSCLC QOD (Arm 6).
- Section 6.4.2.2 Dose Expansion.
- Section 7.4.7 Dermatological Examinations and Photographs.

Change 2: Add inclusion criterion 19, which defines the population eligible for enrollment into the Arm 6 expansion cohort as patients with BRAF non-V600 mutation-positive NSCLC.

The primary change occurs in Section 5.1 Inclusion Criteria:

Added text:

19. Additional inclusion criteria for Arm 6 Expansion Only (MLN2480)

a. Patients with NSCLC who are EGFR, ALK, and ROS negative and have received a minimum of 2 regimens, including a platinum-based regimen and a PD-1/PD-L1 directed agent, unless otherwise contraindicated, and whose tumors harbor non-V600 BRAF mutations, except for the G466V and G469A mutations.

Rationale for Change:

To specify the type of NSCLC and prior treatment requirements for patients to be included in the MLN2480 monotherapy arm (Arm 6).

Change 3: Revise exclusion criterion 15 to include the new Arm 6 expansion cohort.

The primary change occurs in Section 5.2 Exclusion Criteria:

Initial wording:

15. Additional exclusion criteria for Arms 3 and 5 Expansion Only (MLN2480 + paclitaxel; MLN2480 + irinotecan):

Amended or new wording:

15. Additional exclusion criteria for Arms 3**,** ~~and~~ 5**, and 6** Expansion Only (MLN2480 + paclitaxel; MLN2480 + irinotecan**; MLN2480 monotherapy**):

Rationale for Change:

To specify the type of prior treatment requirements for patients to be excluded from the MLN2480 monotherapy arm (Arm 6).

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	20-Feb-2018 19:57 UTC
	Clinical Pharmacology Approval	21-Feb-2018 21:39 UTC