Title: An Open-Label, Phase 1, Dose Escalation Study of MLN2480 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients With Metastatic Melanoma

NCT Number: NCT01425008

Protocol Approve Date: 16 May 2017

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CLINICAL STUDY PROTOCOL C28001 AMENDMENT 9

MLN2480

An Open-Label, Phase 1, Dose Escalation Study of MLN2480 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients With Metastatic Melanoma

Protocol Number:	C28001
Indication:	Solid tumors
Phase:	1
Sponsor:	Millennium Pharmaceuticals, Inc.
Therapeutic Area:	Oncology

Protocol History

Original (Adapted from Biogen Idec)	07 July 2011
Amendment 1	26 September 2011
Amendment 2	28 February 2012
Amendment 3	30 August 2012
Amendment 4	16 November 2012
Amendment 5	14 August 2013
Amendment 6	21 February 2014
Amendment 7	30 September 2014
Amendment 8	22 July 2015
Amendment 9	16 May 2017

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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 9

This document describes the changes in reference to the protocol incorporating Amendment No. 9. The primary reason for this amendment is to reduce the investigational activity, such as scheduled visits and study procedures, for patients in the study for 4 years or longer.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Section 14.12.

Changes in Amendment 9

1. Changed the information for the signatories on the title page.
2. Added a Schedule of Events with reduced assessments (12-week [84-day] treatment cycle) for patients in the study for 4 years or longer.
3. Introduced TAK-580, the new product code for MLN2480.
4. Added that patients in the study for 4 years or longer will take MLN2480 every other day in 12-week (84-day) treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason.
5. Added that when patients have been in the study for 4 years or longer, nonserious adverse events will no longer be reported.
6. Changed the name and telephone number of the call center for product complaints.

PROTOCOL SUMMARY

Study Title: An Open-Label, Phase 1, Dose Escalation Study of MLN2480 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients With Metastatic Melanoma

Study Phase: 1

Name of Principal Investigator: Multicenter, global

Number of Patients: Approximately 198 patients (54 in the Dose Escalation phase, 144 in the Dose Expansion phase)

Study Objectives

Primary

- To evaluate the safety and tolerability of MLN2480 taken orally every other day (Q2D) or weekly (QW) by patients with relapsed or refractory solid tumors (Dose Escalation and Dose Expansion phase and pharmacokinetics [PK] Expansion cohort) or locally advanced, metastatic, and/or unresectable melanoma (Dose Expansion phase)
- To determine the MTD of MLN2480 taken Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation phase)
- To determine the recommended phase 2 dose (RP2D) of MLN2480 taken Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation phase)

Secondary

- To evaluate the preliminary efficacy of MLN2480 as measured by Response Evaluation Criteria in Solid Tumors, version 1.1
- To evaluate the pharmacokinetics of MLN2480
- To evaluate the effect of MLN2480 on pharmacodynamic markers in paired tumor biopsies

Exploratory

CCI

Overview of Study Design: This is a phase 1, multicenter, nonrandomized, open-label, dose escalation study. The study will be conducted in 2 phases. In the Dose Escalation phase, a 3 + 3 dose escalation design will be used to evaluate MLN2480 orally in 2 dose schedules: every other day continuous dosing (Q2D) and once weekly dosing (QW). The Q2D and QW Dose Expansion Phases will test the MTD/RP2D established in the Dose Escalation phase of the corresponding dose schedule.

Q2D Dose Escalation Phase

The Q2D arm will test an initial MLN2480 dose of 20 mg in a 22-day cycle (11 doses), with continuous dosing (no washout). Upon implementation of Amendment 3, any ongoing dose escalation cohort will continue enrollment on the 22-day cycle schedule until the cohort is full and all patients have been evaluated for dose-limiting toxicity (DLT) (see Section 6.2). In all subsequent Q2D cohorts, patients will be treated Q2D on a 28-day cycle (14 doses). Patients who began treatment on the 22-day cycle may switch to the 28-day cycle length upon safety evaluation of the 28-day cycle. Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of MLN2480. Patients may continue treatment for additional cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

Q2D Dose Expansion Phase

Once the MTD and/or RP2D of Q2D MLN2480 have been determined for the 28-day treatment cycle, or at the discretion of the sponsor, the study will continue to a Q2D Dose Expansion phase. The Dose Expansion phase will enroll approximately 96 patients with locally advanced, metastatic, and/or unresectable melanoma and 16 patients with any advanced solid tumor (excluding lymphoma). During expansion, patients with melanoma will be enrolled into 1 of 6 Q2D melanoma expansion cohorts (approximately 16 patients per cohort), based on tumor genotype and treatment history. Individual Dose Expansion cohorts may be opened or closed sequentially or in parallel at the sponsor's discretion, based on emerging data. A seventh cohort in the Dose Expansion phase, the PK Expansion cohort, will enroll a sufficient number of patients (approximately 16) with any advanced solid tumor (excluding lymphoma) to ensure that 12 patients complete protocol-specified dosing and PK assessments scheduled during Cycle 1.

Patients in the Q2D Dose Expansion phase will take MLN2480 orally Q2D for a 28-day cycle until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. Patients in the PK Expansion cohort will take the selected dose of MLN2480 orally Q2D on Days 1-21 of the 28-day cycle for Cycle 1; dosing for Cycle 2 and beyond will follow the standard Q2D dosing in 28-day cycles. The maximum duration of treatment will be 1 year unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

QW Dose Escalation Phase

The QW arm will test an initial MLN2480 dose of 400 mg once weekly (on Days 1, 8, 15, and 22) in a 28-day cycle. Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of MLN2480. Patients may continue treatment for additional cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

QW Dose Expansion Phase

Once the MTD and/or RP2D of QW MLN2480 have been determined, or at the discretion of the sponsor, the study will continue to a QW Dose Expansion phase. The Dose Expansion phase will enroll up to approximately 32 patients (up to 16 patients per cohort) with locally advanced,

metastatic, and/or unresectable melanoma into 1 of 2 QW dose expansion cohorts, based on tumor genotype and treatment history (Cohorts 8 and 9). Individual Dose Expansion cohorts may be opened or closed sequentially or in parallel at the sponsor's discretion, based on emerging data.

Note: Enrollment into Cohort 8 is discontinued as of this amendment (Amendment 8).

Patients in the QW Dose Expansion phase will take MLN2480 orally QW for a 28-day cycle until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 1 year unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

Study Population: This study will be conducted in patients ≥ 18 years of age with advanced solid tumors (excluding lymphoma) (Dose Escalation, Dose Expansion phase, and PK Expansion cohort) or locally advanced, metastatic, and/or unresectable melanoma (Dose Expansion phase).

Dose Escalation Phase:

The Dose Escalation phase will include patients with advanced solid tumors (except lymphoma) who have failed or are not candidates for standard therapies or for whom no approved therapy is available. Tumor tissue is required for all patients at Screening to determine tumor genotype. Sufficient archival tumor tissue or fresh biopsy will meet this requirement. Patients with accessible lesions may additionally be consented for pre- and posttreatment biopsy for pharmacodynamic analysis. The optional posttreatment biopsy on Day 21 (Q2D) or Day 22 (QW) of Cycle 1 should be collected only if an evaluable fresh biopsy was collected at Screening.

Detailed criteria are described in Section 6.3 of the protocol.

Dose Expansion Phase:

The Dose Expansion phase will include patients with locally advanced, metastatic, and/or unresectable melanoma (melanoma expansion cohorts), or advanced solid tumors (excluding lymphoma) (PK Expansion cohort).

Patients with melanoma will be enrolled into 1 of 8 melanoma expansion cohorts, based on tumor genotype and treatment history:

Q2D Melanoma Expansion Cohorts

- Cohort 1: BRAF mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.
- Cohort 2: BRAF mutation-positive cutaneous melanoma, which in response to previous treatment with RAF inhibitors and/or MEK inhibitors, has 1) relapsed following an objective response, 2) failed to demonstrate an objective response, and/or 3) could not tolerate such a regimen due to unacceptable toxicity.
- Cohort 3: NRAS mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.
- Cohort 4: NRAS mutation-positive cutaneous melanoma, which in response to previous treatment with MEK inhibitors, has 1) relapsed following an objective response, 2) failed to demonstrate an objective response, and/or 3) could not tolerate such a regimen due to unacceptable toxicity.
- Cohort 5: BRAF/NRAS mutation-negative cutaneous melanoma (wild type), naïve to any prior anticancer therapy except ipilimumab, anti-PD-1, and anti-PDL-1 mAbs.
- Cohort 6: BRAF/NRAS mutation-negative melanoma (wild type), received at least 1 line of prior anticancer therapy. Melanoma of cutaneous, uveal, or mucosal origin may be enrolled in this cohort.

- (Cohort 7: Not a melanoma cohort. See below for information on the PK expansion cohort)

QW Melanoma Expansion Cohorts;

- Cohort 8: BRAF mutation-positive cutaneous melanoma (approximately 16 patients total: approximately 8 patients who are naïve to prior therapy with RAF and MEK inhibitors, and approximately 8 patients relapsed/refractory to prior therapy with RAF or MEK inhibitors).

Note: Enrollment into Cohort 8 is discontinued as of this amendment (Amendment 8).

- Cohort 9: NRAS mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.

A fresh tumor biopsy for genotyping will be required for all patients in the 6 Q2D dose expansion cohorts and will be requested for QW Expansion cohorts at Screening; archived tumor tissue will also be requested, if available. A postdose fresh biopsy on Day 21 of Cycle 1 will also be collected from at least 8 patients in each Q2D melanoma expansion cohort. The postdose fresh biopsy may need to be collected in more than the specified patients in each cohort/treatment schedule to ensure evaluable biopsies are collected. After the specified pairs of Screening and postdose biopsies have been confirmed to be evaluable from a cohort, the postdose biopsy for the remaining patients in that cohort will be optional. The postdose fresh biopsy should be collected in a patient only if an evaluable fresh biopsy was collected at Screening. For patients on the QW dose schedule, a predose fresh biopsy will be requested on Day 22 of Cycle 1 from at least 8 evaluable patients for pharmacodynamic assessment. Evaluable biopsy pairs collected at Screening and Day 21 (Q2D) or Day 22 (QW) of Cycle 1 will be used for pharmacodynamic biomarker analysis.

A seventh Q2D expansion cohort, the PK Expansion cohort, will enroll patients with any advanced solid tumor (excluding lymphoma, but including melanoma) who have failed or are not candidates for standard therapies or for whom no approved therapy is available. In addition to contributing to the evaluation of safety, tolerability, and preliminary antitumor activity, the PK Expansion cohort will be used to more fully characterize MLN2480 PK. Archived or fresh tumor will be obtained at Screening for genotyping. No paired biopsies for pharmacodynamic analysis will be collected in the PK Expansion cohort.

Detailed criteria are described in Section 6.4 of the protocol.

Number of Study Center(s): Approximately 14 to 22 study sites (approximately 4 to 8 sites in the United States [US] for the Dose Escalation phase and approximately 10 to 18 US and International sites for the Dose Expansion phase.)

Duration of Study: The study period will consist of the Screening and Treatment periods.

During the Screening period, patient eligibility for the study will be determined within 28 days prior to Day 1. During the Treatment period, patients will take MLN2480 orally Q2D in 22- or 28-day treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

When patients discontinue study treatment, they should return to the study site 30 days after administration of the last dose of study drug to complete the End of Study visit procedures.

All MLN2480-related toxicities will be followed until the End of Study visit or until the toxicities have resolved, stabilized, or returned to baseline, whichever occurs later.

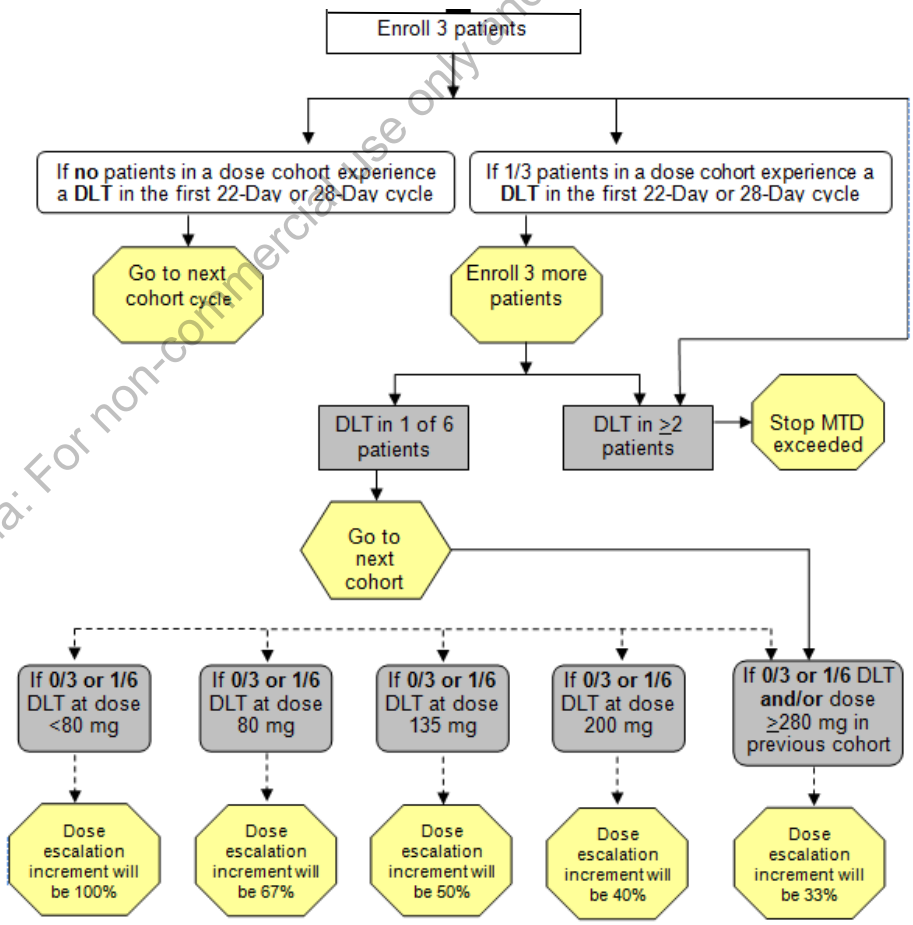
Dose Escalation Algorithm

Q2D Dose Escalation Phase

The Q2D dose escalation will follow a modified Fibonacci schema (sequential dose escalation increments of approximately 100%, 100%, 67%, 50%, 40%, and 33% thereafter; see Table 6-1).

When the cycle length is changed from 22 days to 28 days (per Amendment 3), the same unit dose of the previously tolerated cohort at the 22-day schedule will be repeated for the first cohort at 28 days. After tolerability is confirmed when the same unit dose is administered every other day (Q2D) in a 28-day cycle instead of a 22-day cycle, subsequent dose escalations in a 28-day cycle will consist of a 33% increase in both unit and total cycle dose. If an MTD is established in the 22-day cycle before transition to the 28-day cycle has occurred, the MTD and/or RP2D will be confirmed in the 28-day cycle.

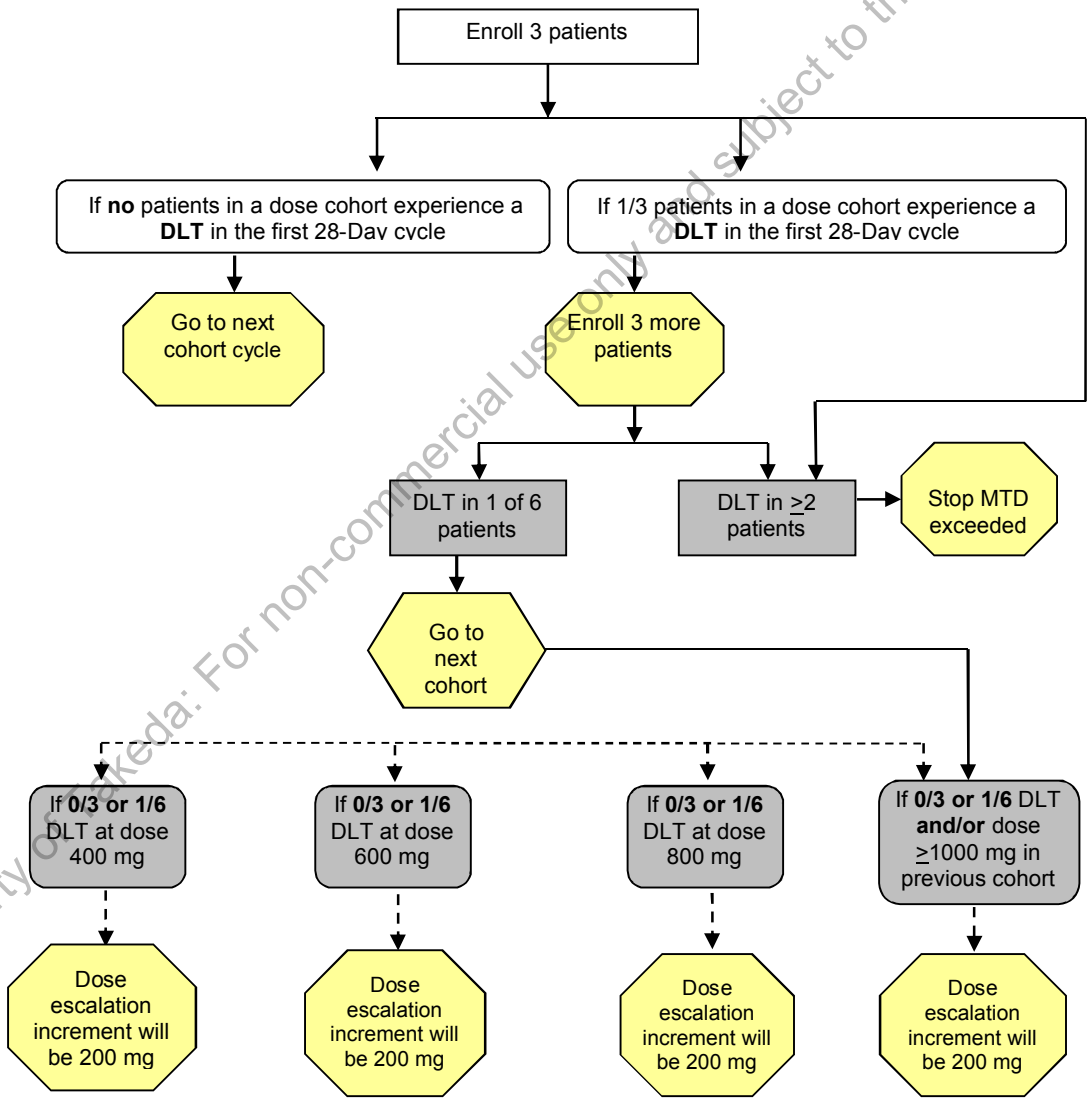
In the absence of more than 1 dose-limiting toxicity (DLT) occurring in a given cohort or the maximum tolerated dose (MTD) being established, it is anticipated that the MLN2480 doses for the sequential Q2D cohorts will be 20, 40, 80, 135, 200, and 280 mg Q2D, with 33% dose escalation increments thereafter until the Q2D MTD is established. Depending on the nature of the DLTs in the preceding dose cohort, an additional **intermediate dose cohort** may be evaluated before proceeding to the Q2D Dose Expansion phase of the study.



QW Dose Escalation Phase

The QW dose escalation phase (added per amendment 6) will test doses of MLN2480 on Days 1, 8, 15, and 22 of a 28-day cycle. Based on safety and pharmacokinetic (PK) information learned from the Q2D Dose Escalation phase, a starting dose of 400 mg will be used in this phase. In the absence of more than 1 dose-limiting toxicity (DLT) occurring in a given cohort or the maximum tolerated dose (MTD) being established, it is anticipated that the MLN2480 doses for the sequential QW cohorts will be 400, 600, 800, and 1000 mg, with 200 mg dose escalation increments thereafter until the QW MTD is established. For the initial dose increase (from 400 mg to 600 mg), patients will be enrolled in the 600 mg dose cohort in a staggered manner, with 1 week in between each patient.

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 MLN2480.



In the event that less than dose proportional increases in systemic exposure are observed

during further dose escalation of MLN2480 in the QW dosing regimen, alternative QW dosing regimens may be explored to increase systemic exposures. This could include splitting a weekly dose in AM and PM (approximately 12-hr apart) on Day 1, 8, 15, and 22 or splitting a weekly dose on Days 1 and 2, Days 8 and 9, Days 15 and 16, Days 22 and 23. The PK and ECG sampling schedule for alternative QW dosing regimens are listed in the Pharmacokinetic and Electrocardiogram Sampling Schedule E: Alternative (Split Dose, Same Day) QW Dose Escalation and Dose Expansion Phases and in the Pharmacokinetic and Electrocardiogram Sampling Schedule F: Alternative (Split Dose, Sequential Days) QW Dose Escalation and Dose Expansion Phases.

Q2D Schedules of Events

Q2D 28-Day Treatment Cycle: Cycle 1 Schedule															
	Screening	**Day 1**						**Day 21**							
	≤ 28 Days Before Day 1	**Pre dose**	**Post dose**	**Day 2**	**Day 3**	**Day 9**	**Day 15**	**Pre dose**	**Post dose**	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 28**
Informed consent form	X														
Inclusion/exclusion criteria	X														
Demographics	X														
Medical history[b]	X														
Complete physical examination, height, and body weight measurement	X	X[a]													
Dermatological examination with documentation of any suspicious lesions[c]	X	X[c]				X[c,d]	X[c,d]			X[c,d]					
Digital photographs of skin[c]	X														
ECHO or MUGA	X														
12-lead ECG for safety (all patients) [e]	X														
12-lead triplicate ECG (Dose Escalation phase)[e]		X	X		X			X	X						
12-lead triplicate ECG (PK Expansion		X	X		X			X	X		X		X		

Q2D 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21							
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 9	Day 15	Pre dose	Post dose	Day 22	Day 23	Day 24	Day 25	Day 26	Day 28
cohort)[d]															
Vital signs (temperature, blood pressure, pulse rate)[f]	X	X[g]	X[g]			X[g]	X[g]								
ECOG performance status	X	X[a]													
Laboratory tests															
Hematology[h]	X	X[a, i]				X	X	X							
Blood chemistry[j]	X	X[a, i]				X	X	X							
Bone marrow aspirate and biopsy[k,l]															
Coagulation[m]	X								X						
Thyroid function	X														
Pregnancy test (female patients of reproductive potential)	X[a]	X[a,n]													
Urinalysis[n]	X	X[o]													
CCI [redacted]															
CCI [redacted]															

Q2D 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21							
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 9	Day 15	Pre dose	Post dose	Day 22	Day 23	Day 24	Day 25	Day 26	Day 28
CCI															
Blood sample for PK assessment (Dose Escalation phase)[q,r]		X	X	X	X	X	X	X	X	X	X				
Blood sample for PK assessment (PK Expansion cohort)[r,s]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for PK assessment (melanoma expansion cohorts)[r,t, u]		X	X			X		X	X	X					
Urine samples for PK assessment (Dose Escalation phase)[v]		X							X						
CCI															
Fresh tumor biopsy[k]	X								X						
Disease assessment, including CT or MRI scan[x]	X[w]														
Concomitant therapy and procedures recording[y]	X	Concomitant therapy and procedures must be recorded from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever comes first.													

Q2D 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21							
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 9	Day 15	Pre dose	Post dose	Day 22	Day 23	Day 24	Day 25	Day 26	Day 28
AE reporting			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.												
	SAEs[y] will be collected from signing of the informed consent form through 30 days after the last dose of study drug.														
MLN2480 administration															
Q2D dose escalation phase[z]		MLN2480 dosing once every 2 days on Days 1-28 of a 28-day cycle (14 doses), starting on Day 1													
Q2D melanoma expansion cohorts)[z]		MLN2480 dosing once every 2 days on Days 1-28 of a 28-day cycle (14 doses), starting on Day 1													
Q2D PK Expansion cohort[aa]		MLN2480 dosing once every 2 days on Days 1-21 of a 28-day-cycle (11 doses) starting on Day 1, followed by a 1-week treatment-free period (Days 22-28)													

Abbreviations: aPTT=activated partial thromboplastin time; AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRF=Case Report Form; CT=computed tomography; DLT=dose-limiting toxicity; ECG=Electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI ; ICF=informed consent form; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition [scan]; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; SAE=serious adverse event; WBC=white blood cell.

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).

a Assessments need not be repeated if Screening assessments were performed within 72 hours before MLN2480 dosing, unless otherwise specified. Height is to be collected at Screening only.

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 All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. Assessments need not be repeated if the prior assessment was performed within 72 hours. The examination for skin lesions will include the entire skin. At Screening, a complete dermatological exam will be performed and digital photographs will be taken to document patients' baseline skin prior to treatment. Existing lesions will be monitored

Q2D 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21							
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 9	Day 15	Pre dose	Post dose	Day 22	Day 23	Day 24	Day 25	Day 26	Day 28

throughout the study and changes to the lesions will be recorded in the CRF and documented in digital photographs. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

d Assessment will be performed on the study day specified ± 5 days.

e A single 12-lead ECG will be collected at Screening in all patients to assess eligibility. Triplicate 12-lead ECGs will be collected as indicated in Table 1-3 and Table 1-6 for the Dose Escalation phase and PK Expansion cohorts, respectively. The triplicate ECG measurements should be completed after a 5-minute rest period in a supine position and will be recorded at 2 to 5 minute intervals immediately before the corresponding PK blood draw.

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

g On Days 1, 9, and 15 vital sign measurements will be performed within 15 minutes prior to dosing. On Cycle 1, Day 1 only, also perform vital sign measurements at 2 hours ± 10 minutes and 6 hours ± 10 minutes postdose.

h Hematology will be tested at local laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 platelet counts return to > 50,000/µL.

i Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts [only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion], absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle.

j Blood chemistry results will include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

k Bone marrow aspirate and biopsy will be encouraged only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

l Fresh biopsy of tumor is required for all patients in the 6 Q2D melanoma expansion cohorts at Screening. The Screening tumor biopsy must be immediately formalin fixed, paraffin embedded, and have 5 slides cut from the block to be used for genetic analysis. The tissue on the slides must contain at least 4 mm^2 tissue area with a minimum of 10% tumor content. A postdose fresh biopsy on Day 21 (3-9 hrs postdose) of Cycle 1 will also be collected from at least 8 patients in each Q2D melanoma expansion cohort, to ensure 8 evaluable biopsies are collected in each cohort. After 8 pairs of Screening and Day 21 biopsies have been confirmed to be evaluable from a cohort, the Day 21 biopsy for the remaining patients in that cohort will be optional. If possible, the Day 21 biopsy should be from the same lesion biopsied during Screening; however, an alternative lesion may be used if this is not possible. A fresh biopsy is required at Screening for patients in the Dose Escalation and PK Expansion cohorts if an archival tumor tissue sample is unavailable, inadequate, or was

Q2D 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21							
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 9	Day 15	Pre dose	Post dose	Day 22	Day 23	Day 24	Day 25	Day 26	Day 28

obtained more than 24 months prior to Screening. A postdose fresh biopsy on Day 21 (3-9 hours postdose) of Cycle 1 is optional for patients in the Dose Escalation phase if an evaluable biopsy was obtained at Screening (Table 1-13).

m Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be > 75,000/mm^3.

n A urine or serum pregnancy test is permitted at this time point (C1D1) only. The Screening and EOS pregnancy tests must be serum.

o Urinalysis includes dipstick for blood, protein, pH, Specific gravity, Ketones, Bilirubin, Nitrite, Urobilinogen, Leukocytes and glucose (microscopic examination, if abnormal). Samples will be collected predose.

p CCI

q CCI

r Refer to Table 1-1 for time points at which blood samples will be collected for PK assessments in the Dose Escalation phase. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

s In addition to the scheduled PK sample collections, a blood sample to measure MLN2480 plasma concentrations 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.

t Refer to Table 1-4 for time points at which blood samples will be collected for PK assessments in the PK Expansion cohort. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

u Refer to Table 1-7 for time points at which blood samples will be collected for PK assessments in the Q2D melanoma expansion cohorts of the Dose Expansion phase. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

v Refer to Table 1-2 and Table 1-5 for time points at which urine samples will be collected for PK assessments in the Dose Escalation phase and the PK Expansion cohort, respectively.

w CCI

x Refer to Section 7.4.15 and Section 14.3.

y Concomitant therapies and procedures must be recorded from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever comes first. Refer to Section 6.6.1 for prohibited medications and therapies and Section 6.6.2.3 for medications or procedures that are restricted or should be used cautiously.

Q2D 28-Day Treatment Cycle: Cycle 1 Schedule															
	Screening	**Day 1**						**Day 21**							
	≤ 28 Days Before Day 1	**Pre dose**	**Post dose**	**Day 2**	**Day 3**	**Day 9**	**Day 15**	**Pre dose**	**Post dose**	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 28**

z Including serious pretreatment events; see Section 9.

aa On dosing days when the patient does not have a clinic visit (ie, Days 5, 7, 11, 13, 17, and 19), patients will take their dose of MLN2480 at home.

bb For all subsequent cycles beyond Cycle 1, dosing in the PK Expansion cohort will be once every 2 days for a 28-day cycle.

Q2D 28-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 28)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**
Physical examination and body weight measurement	X		
Dermatological examination with documentation of any suspicious lesions[a]	X		X
ECHO or MUGA			X
12-lead Single ECG for Safety (melanoma expansion cohorts)	X		
12-lead Triplicate ECG (Dose Escalation Phase and PK Expansion cohort)[b]	X		
Vital signs (temperature, blood pressure, pulse rate)[c]	X	X	
Laboratory tests			
Hematology[d]	X[e]	X	
Blood chemistry[f]	X[e]	X	
Bone marrow aspirate and biopsy[g]			
Coagulation[h]			
Thyroid function	X		
Urinalysis[i]	X		

Q2D 28-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 28)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**
Plasma samples for biomarker assessment and circulating tumor DNA	X[j]		
Blood samples for PK assessment (All patients)	X[k, l]		
Disease assessment, including CT or MRI scan			X[m]
Concomitant therapy and procedures recording[n]	Concomitant therapy and procedures must be recorded from Screening through the End of Study visit or start of subsequent antineoplastic therapy, whichever comes first.		
AE reporting	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.		
	SAEs will be collected from signing of the informed consent form through 30 days after the last dose of study drug.[o]		
MLN2480 Q2D administration (all patients)[p]	MLN2480 dosing is once every 2 days on Days 1-28 of a 28 day cycle (14 doses)		

Abbreviations: aPTT=activated partial thromboplastin time; AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CT=computed tomography; ECG=Electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition [scan]; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WBC=white blood cell.

a All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. Assessments need not be repeated if the prior assessment was performed within 72 hours. The examination for skin lesions will include the entire skin. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

b The triplicate ECG measurements should be completed after a 5-minute rest period in the supine position and at 2- to 5-min intervals immediately before the corresponding PK blood draw. The triplicate ECGs will be collected predose (within 1 hour prior to dosing; see Table 1-3)

c Perform vital signs measurement within 15 minutes prior to dosing. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d Hematology will be tested at local and central laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 > 1,000/µL and platelet counts return to > 50,000/µL.

e Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts, absolute differential, and ANC) and

Q2D 28-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 28)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**

blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle. Hematology and blood chemistry for Cycle 2, Day 1 may be completed up to 72 hours prior to Day 1.

f Blood chemistries will be tested at local laboratories and include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

g Bone marrow aspirate and biopsy will be encouraged for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

h Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be >75,000/mm^3.

i Urinalysis includes dipstick for blood, protein, and glucose (microscopic examination, if abnormal). Samples will be collected predose.

j Sample should be collected within 1 hour prior to MLN2480 dosing on Cycle 2, Day 1.

k Refer to Tables 1-1, 1-4, and 1-7 for time points at which blood samples will be collected for PK assessments in the Q2D Dose Escalation Phase, PK Expansion cohort, and Q2D melanoma expansion cohorts, respectively. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

l In addition to the scheduled PK sample collections, a blood sample to measure MLN2480 plasma concentrations 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.

m Disease assessments (including CT or MRI scans of all sites of disease) will be performed every 2 cycles after starting MLN2480 treatment, beginning on Cycle 2, Day 27 ± 2 days. Any complete response or partial response must be confirmed at least 4 weeks after the response is first documented. Clinical response and disease progression will be evaluated using RECIST, version 1.1, per investigator assessment.

n Concomitant therapies and procedures must be recorded from Screening through the End of Study visit or until the start of subsequent antineoplastic therapy, whichever occurs first. Refer to Section 6.6.1 for prohibited medications and therapies and Section 6.6.2.3 for medications or procedures that are restricted or should be used cautiously.

o Including serious pretreatment events; see Section 9.

p Patients will take MLN2480 orally once every 2 days and will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose. On dosing days when the patient does not have a clinic visit (ie, Days 3, 5, 7, 9, 11, 13, 17, 19, 21, 23, and 25), patients will take their dose of MLN2480 at home.

Q2D 28-Day Treatment Cycle: Cycle 3 and Subsequent Cycles Schedule				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 28)			**End of Study Visit[a]**
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**	
Physical examination and body weight measurement	X			X
Dermatological examination with documentation of any suspicious lesions[b]			X	X[b]
ECHO or MUGA			X[c]	
Single 12-Lead ECG for Safety (all patients)[d]	X			X
Vital signs (temperature, blood pressure, pulse rate)[e]	X	X		X
ECOG performance Status				X
Laboratory tests				
Hematology[f]	X[g]	X		X
Blood chemistry[h]	X[g]	X		X
Bone marrow aspirate and biopsy[i]				
Coagulation[j]				
Thyroid function	X			X
Serum pregnancy test (female patients of reproductive potential)				X
Urinalysis[k]	X			X
Disease assessment, including CT or MRI scan			X[l]	X[m]
Plasma samples for biomarker assessment and circulating tumor DNA	X[n]			X
Concomitant therapy and procedures recording[o]	Concomitant therapy and procedures must be recorded from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever comes first.			
AE reporting	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			
	SAEs will be collected from signing of the informed consent form through 30 days after the last dose of study drug[p]			

Q2D 28-Day Treatment Cycle: Cycle 3 and Subsequent Cycles Schedule				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 28)			**End of Study Visit[a]**
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**	
MLN2480 Q2D administration[q]	MLN2480 dosing is once every 2 days on Days 1-28 of a 28-day cycle (14 doses)			

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRF=case report form; CT=computed tomography; ECG=Electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition [scan]; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WBC=white blood cell

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. Patients who discontinue study treatment early should complete the End of Study visit 30 (+ 10) days after the last dose of study treatment.

b All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. Assessments need not be repeated if the prior assessment was performed within 72 hours. The examination for skin lesions will include the entire skin. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

c 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).

d A single 12-lead ECG will be collected predose on Day 1 and at the EOS visit. When the timing of a blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

e Predose (within 15 minutes prior to dosing; except at End of Study visit where no study drug is administered). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

f Hematology will be tested at local laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 platelet counts return to > 50,000/µL.

g Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts, absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle. Hematology and blood chemistry for Cycle 3 and subsequent cycles Day 1 may be completed up to 72 hours prior to Day 1.

h Blood chemistry results include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

i Bone marrow aspirate and biopsy will be encouraged for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

j Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone

Q2D 28-Day Treatment Cycle: Cycle 3 and Subsequent Cycles Schedule				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 28)			**End of Study Visit[a]**
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**	

marrow biopsies, platelet count should be >75,000/mm^3.

k Urinalysis includes dipstick for blood, protein, and glucose (microscopic examination, if abnormal). Samples will be collected predose.

l Disease assessments (including CT or MRI scans of all sites of disease) will be performed every 8 weeks ± 2 days after starting MLN2480 treatment, beginning on Cycle 2, Day 27 ± 2 days. Any complete response or partial response must be confirmed at least 4 weeks after the response is first documented. Clinical response and disease progression will be evaluated using RECIST, version 1.1 (see Section 14.3), per investigator assessment.

m Disease assessments need not be repeated if performed within 4 weeks prior to the End of Study visit.

n On Cycle 3, Day 1 and beyond, the predose plasma sample will be taken within 1 hour prior to MLN2480 dosing.

o Concomitant therapies and procedures must be recorded from Screening through the End of Study visit or until the start of subsequent antineoplastic therapy, whichever occurs first. Refer to Section 6.6.1 for prohibited medications and therapies and Section 6.6.2.3 for medications or procedures that are restricted or should be used cautiously.

p Including serious pretreatment events; see Section 9.

q Patients will take MLN2480 orally once every 2 days and will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose. On dosing days when the patient does not have a clinic visit (ie, Days 3, 5, 7, 9, 11, 13, 17, 19, 21, 23, and 25), patients will take their dose of MLN2480 at home.

QW Schedules of Events

QW 28-Day Treatment Cycle: Cycle 1 Schedule																	
	Screening	**Day 1**									**Day 22**						
	≤ 28 Days Before Day 1	**Pre dose**	**Post dose**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 7**	**Day 8**	**Day 15**	**Pre dose**	**Post dose**	**Day 23**	**Day 24**	**Day 25**	**Day 27**	**Day 28**
Informed consent form	X																
Inclusion/exclusion criteria	X																
Demographics	X																
Medical history	X																
Complete physical examination, height, and body weight measurement	X	X[a]															
Dermatological examination with documentation of any suspicious lesions[c]	X	X							X[c]	X[c]	X[c]						
Digital photographs of skin[b]	X																
ECHO or MUGA	X																
12-lead ECG for safety (all patients) [d]	X																
12-lead triplicate ECG (Dose Escalation phase)[d]		X	X								X	X					
Vital signs	X	X[f]	X[f]						X[f]	X[f]							

QW 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1									Day 22						
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8	Day 15	Pre dose	Post dose	Day 23	Day 24	Day 25	Day 27	Day 28
(temperature, blood pressure, pulse rate)[e]																	
ECOG performance status	X	X[a]															
Laboratory tests																	
Hematology[g]	X	X[a,h]							X	X	X						
Blood chemistry[i]	X	X[a,h]							X	X	X						
Bone marrow aspirate and biopsy[j]																	
Coagulation[k]	X											X					
Thyroid function	X																
Pregnancy test (female patients of reproductive potential)	X[a]	X[a,l]															
Urinalysis[m]	X	X[a]															
CCI [redacted]																	
CCI [redacted]																	

QW 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1									Day 22						
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8	Day 15	Pre dose	Post dose	Day 23	Day 24	Day 25	Day 27	Day 28
Blood sample for PK Sampling Schedule D (QW dosing; Dose Escalation & Dose Expansion phases)[p,q]		X	X	X	X		X		X	X	X	X	X	X		X	
Blood sample for PK Sampling Schedule E (QW BID dosing; Dose Escalation & Dose Expansion phases)[q,r]		X	X						X		X	X	X	X		X	
Blood sample for PK Sampling Schedule F (QW split 2-day dosing; Dose Escalation & Dose Expansion phases)[q,s]		X	X	X	X	X		X	X	X	X	X	X	X	X		X
Urine samples for PK assessment (QW and QW BID; Dose Escalation phase)[t]		X										X[u]					
Urine samples for PK assessment		X											X[u]				

QW 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1									Day 22						
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8	Day 15	Pre dose	Post dose	Day 23	Day 24	Day 25	Day 27	Day 28
(QW split 2-day dosing; Dose Escalation phase)[t]																	
CCI [redacted]																	
Fresh tumor biopsy[w]	X										X						
Disease assessment, including CT or MRI scan	X[x]																
Concomitant therapy and procedures recording[y]	Concomitant therapy and procedures must be recorded from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever comes first.																
AE reporting			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.														
	SAEs will be collected from signing of the informed consent form through 30 days after the last dose of study drug.[z]																
MLN2480 administration (Dose Escalation and Dose Expansion phases)[aa]																	
QW dosing			MLN2480 dosing weekly, on Days 1, 8, 15, and 22 of a 28-day cycle (4 doses), starting on Day 1														
QW BID dosing			MLN2480 dosing weekly, BID, on Days 1, 8, 15, and 22 of a 28-day cycle (8 doses), starting on Day 1														
QW split 2-day dosing			MLN2480 dosing weekly, on Days 1 & 2, 8 & 9, 15 & 16, and 22 & 23 of a 28-day cycle (8 doses), starting on Day 1														

Abbreviations: aPTT=activated partial thromboplastin time; AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRF=Case Report Form; CT=computed tomography; DLT=dose-limiting toxicity; ECG=Electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI [redacted]; ICF=informed consent form; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition [scan]; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; SAE=serious adverse event; WBC=white blood cell.

QW 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1									Day 22						
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8	Day 15	Pre dose	Post dose	Day 23	Day 24	Day 25	Day 27	Day 28

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).

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.

a Assessments need not be repeated if Screening assessments were performed within 72 hours before MLN2480 dosing, unless otherwise specified. Height is to be collected at Screening only.

b All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. Assessments need not be repeated if the prior assessment was performed within 72 hours. The examination for skin lesions will include the entire skin. At Screening, a complete dermatological exam will be performed and digital photographs will be taken to document patients' baseline skin prior to treatment. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF and documented in digital photographs. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

c Assessment will be performed on the study day specified ± 5 days.

d A single 12-lead ECG will be collected at Screening in all patients to assess eligibility. Triplicate 12-lead ECGs will be collected as indicated in Table 1-12 for the QW Dose Escalation phase. The triplicate ECG measurements should be completed after a 5-minute rest period in a supine position and will be recorded at 2 to 5 minute intervals immediately before the corresponding PK blood draw.

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

f On Days 1, 8, and 15 vital sign measurements will be performed within 15 minutes prior to dosing. On Cycle 1, Day 1 only, also perform vital sign measurements at 2 hours ± 10 minutes and 6 hours ± 10 minutes postdose.

g Hematology will be tested at local laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 platelet counts return to > 50,000/µL.

h Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts [only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion], absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle.

i Blood chemistry results will include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

QW 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1									Day 22						
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8	Day 15	Pre dose	Post dose	Day 23	Day 24	Day 25	Day 27	Day 28

j Bone marrow aspirate and biopsy will be encouraged only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

k Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be > 75,000/mm^3.

l A urine or serum pregnancy test is permitted at this time point (C1D1) only. The Screening and EOS pregnancy tests must be serum.

m Urinalysis includes dipstick for blood, protein, pH, Specific gravity, Ketones, Bilirubin, Nitrite, Urobilinogen, Leukocytes and glucose (microscopic examination, if abnormal). Samples will be collected predose.

n CCI [redacted]

o CCI [redacted]

p See Pharmacokinetic and Electrocardiogram Sampling Schedule D: QW Dose Escalation and Dose Expansion Phases and Table 1-8 for time points at which blood samples will be collected for PK assessments. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

q In addition to the scheduled PK sample collections, a blood sample to measure MLN2480 plasma concentrations 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.

r If the QW BID dosing schedule is explored to increase systemic exposures, see Pharmacokinetic and Electrocardiogram Sampling Schedule E: Alternative (Split Dose, Same Day) QW Dose Escalation and Dose Expansion Phases and Table 1-9 for time points at which blood samples will be collected for PK assessments. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

s If the QW split 2-day dosing schedule is explored to increase systemic exposures, see Pharmacokinetic Sampling Schedule F: Alternative (Split Dose, Sequential Days) QW Dose Escalation and Dose Expansion Phases and Table 1-10 for time points at which blood samples will be collected for PK assessments. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

t Refer to Table 1-11 for time points at which urine samples will be collected for PK assessments.

u Timing for QW PK assessments depends on which QW schedule is being followed. See Table 1-8 through Table 1-12 for more information.

v CCI [redacted]

w A fresh or archival biopsy of tumor is required for all patients in the 2 dose expansion cohorts at Screening. The Screening tumor biopsy must be immediately formalin fixed, paraffin embedded, and have 5 slides cut from the block to be used for genetic analysis. The tissue on the slides must contain at least 4 mm^2 tissue area with a minimum of 10% tumor content. Paired fresh tumor biopsies at Screening and on Day 22 of Cycle 1 will also be collected from at least 8

QW 28-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1								Day 22						
	≤ 28 Days Before Day 1	Pre dose	Post dose	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8	Day 15	Pre dose	Post dose	Day 23	Day 24	Day 25	Day 27	Day 28

evaluable patients. After 8 pairs of Screening and Day 22 biopsies have been confirmed to be evaluable from a cohort, the Day 22 biopsy for the remaining patients in that cohort will be optional. If possible, the Day 22 biopsy should be from the same lesion biopsied during Screening; however, an alternative lesion may be used if this is not possible. A fresh biopsy may be required at Screening for patients if an archival tumor tissue sample is unavailable, inadequate, or was obtained more than 24 months prior to Screening. A fresh biopsy on Day 22 of Cycle 1 is optional for patients in the Dose Escalation phase if an evaluable fresh biopsy was obtained at Screening (see Table 1-13 for more information).

x Refer to Section 7.4.15 and Section 14.3.

y Refer to Section 6.6.1 for prohibited medications and therapies and Section 6.6.2.3 for medications or procedures that are restricted or should be used cautiously.

z Including serious pretreatment events; see Section 9.

aa Timing for QW dosing depends on depends on which QW schedule is being followed. See Table 1-8 through Table 1-12 for more information. Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose.

QW 28-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 28)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**
Physical examination and body weight measurement	X		
Dermatological examination with documentation of any suspicious lesions[a, b]	X		X
ECHO or MUGA			X
12-lead Single ECG for Safety (all patients)	X		
Vital signs (temperature, blood pressure, pulse rate)[c]	X	X	
Laboratory tests			
Hematology[d]	X[e]	X	
Blood chemistry[f]	X[e]	X	
Bone marrow aspirate and biopsy	At time of recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion[g]		
Coagulation[h]			
Thyroid function	X		
Urinalysis[i]	X		
Plasma samples for biomarker assessment and circulating tumor DNA	X[j]		
Blood samples for PK assessment (All patients)	X[k, l]		
Disease assessment, including CT or MRI scan			X[m]
Concomitant therapy and procedures recording[n]	Concomitant therapy and procedures must be recorded from Screening through the End of Study visit or start of subsequent antineoplastic therapy, whichever comes first.		
AE reporting	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.		
	SAEs will be collected from signing of the informed consent form through 30 days after the last dose of study drug.[o]		
MLN2480 QW administration[p]	MLN2480 dosing is once weekly on Days 1, 8, 15, and 22 of a 28-day cycle (4 doses)		
QW dosing	MLN2480 dosing weekly, on Days 1, 8, 15, and 22 of a 28-day cycle (4 doses), starting on Day 1		

QW 28-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 28)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**
QW BID dosing	MLN2480 dosing weekly, BID, on Days 1, 8, 15, and 22 of a 28-day cycle (8 doses), starting on Day 1		
QW split 2-day dosing	MLN2480 dosing weekly, on Days 1 & 2, 8 & 9, 15 & 16, and 22 & 23 of a 28-day cycle (8 doses), starting on Day 1		

Abbreviations: aPTT=activated partial thromboplastin time; AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CT=computed tomography; ECG=Electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition [scan]; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WBC=white blood cell.

a Assessments need not be repeated if the prior assessment was performed within 72 hours.

b All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. The examination for skin lesions will include the entire skin. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

c Perform vital signs measurement within 15 minutes prior to dosing. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d Hematology will be tested at local and central laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 platelet counts return to > 50,000/µL.

e Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts, absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle. Hematology and blood chemistry for Cycle 2, Day 1 may be completed up to 72 hours prior to Day 1.

f Blood chemistries will be tested at local laboratories and include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

g Bone marrow aspirate and biopsy will be encouraged for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

h Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be > 75,000/mm^3.

i Urinalysis includes dipstick for blood, protein, and glucose (microscopic examination, if abnormal). Samples will be collected predose.

j Sample should be collected within 1 hour prior to MLN2480 dosing on Cycle 2, Day 1.

QW 28-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 28)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**

k Refer to Table 1-8, Table 1-9, and Table 1-10 for time points at which blood samples will be collected for PK assessments in the QW Dose Escalation and Dose Expansion phases. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

l In addition to the scheduled PK sample collections, a blood sample to measure MLN2480 plasma concentrations 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.

m Disease assessments (including CT or MRI scans of all sites of disease) will be performed every 2 cycles after starting MLN2480 treatment, beginning on Cycle 2, Day 27 ± 2 days. Any complete response or partial response must be confirmed at least 4 weeks after the response is first documented. Clinical response and disease progression will be evaluated using RECIST, version 1.1, per investigator assessment.

n Refer to Section 6.6.1 for prohibited medications and therapies and Section 6.6.2.3 for medications or procedures that are restricted or should be used cautiously.

o Including serious pretreatment events; see Section 9.

p Timing for QW dosing depends on depends on which QW schedule is being followed. See Table 1-8 through Table 1-12 for more information. Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose.

QW 28-Day Treatment Cycle: Cycle 3 and Subsequent Cycles Schedule				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 28)			**End of Study Visit[a]**
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**	
Physical examination and body weight measurement	X			X
Dermatological examination with documentation of any suspicious lesions[b]			X	X[b]
ECHO or MUGA			X[c]	
Single 12-lead ECG for safety (all patients)[d]	X			X
Vital signs (temperature, blood pressure, pulse rate)[e]	X	X		X
ECOG performance status				X
Laboratory tests				
Hematology[f]	X[g]	X		X
Blood chemistry[h]	X[g]	X		X
Bone marrow aspirate and biopsy[i]				
Coagulation[j]				
Thyroid function	X			X
Serum pregnancy test (female patients of reproductive potential)				X
Urinalysis[k]	X			X
Disease assessment, including CT or MRI scan			X[l]	X[m]
Plasma samples for biomarker assessment and circulating tumor DNA	X[n]			X
Concomitant therapy and procedures recording[o]	Concomitant therapy and procedures must be recorded from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever comes first.			
AE reporting	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			
	SAEs will be collected from signing of the informed consent form through 30 days after the last dose of study drug[p]			
MLN2480 QW administration[q]				

QW 28-Day Treatment Cycle: Cycle 3 and Subsequent Cycles Schedule				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 28)			**End of Study Visit[a]**
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**	
QW dosing	MLN2480 dosing weekly, on Days 1, 8, 15, and 22 of a 28-day cycle (4 doses), starting on Day 1			
QW BID dosing	MLN2480 dosing weekly, BID, on Days 1, 8, 15, and 22 of a 28-day cycle (8 doses), starting on Day 1			
QW split 2-day dosing	MLN2480 dosing weekly, on Days 1 & 2, 8 & 9, 15 & 16, and 22 & 23 of a 28-day cycle (8 doses), starting on Day 1			

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRF=case report form; CT=computed tomography; ECG=Electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition [scan]; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WBC=white blood cell

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. Patients who discontinue study treatment early should complete the End of Study visit 30 (+10) days after the last dose of study treatment.

b All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. Assessments need not be repeated if the prior assessment was performed within 72 hours. The examination for skin lesions will include the entire skin. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

c 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).

d A single 12-lead ECG will be collected predose on Day 1 and at the EOS visit. When the timing of a blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

e Predose (within 15 minutes prior to dosing; except at End of Study visit where no study drug is administered). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

f Hematology will be tested at local laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 platelet counts return to > 50,000/µL.

g Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts, absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle. Hematology and blood chemistry for Cycle 3 and subsequent cycles Day 1 may be completed up to 72 hours prior to Day 1.

h Blood chemistry results include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase,

QW 28-Day Treatment Cycle: Cycle 3 and Subsequent Cycles Schedule				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 28)			End of Study Visit[a]
Tests and Assessments	**Day 1 ± 2 Days**	**Day 15 ± 2 Days**	**Day 27 ± 2 Days**	

AST, ALT, albumin, and calcium.

i Bone marrow aspirate and biopsy will be encouraged for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

j Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be >75,000/mm^3.

k Urinalysis includes dipstick for blood, protein, and glucose (microscopic examination, if abnormal). Samples will be collected predose.

l Disease assessments (including CT or MRI scans of all sites of disease) will be performed every 8 weeks ± 2 days after starting MLN2480 treatment, beginning on Cycle 2, Day 27 ± 2 days. Any complete response or partial response must be confirmed at least 4 weeks after the response is first documented. Clinical response and disease progression will be evaluated using RECIST, version 1.1 (see Section 14.3), per investigator assessment.

m Disease assessments need not be repeated if performed within 4 weeks prior to the End of Study visit.

n On Cycle 3, Day 1 and beyond, the predose plasma sample will be taken within 1 hour prior to MLN2480 dosing.

o Refer to Section 6.6.1 for prohibited medications and therapies and Section 6.6.2.3 for medications or procedures that are restricted or should be used cautiously.

p Including serious pretreatment events; see Section 9.

q Timing for QW dosing depends on depends on which QW schedule is being followed. See Table 1-8 through Table 1-12 for more information. Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose.

12-Week (84-Day) Treatment Cycle for Patients in the Study for 4 Years or Longer

Tests and Assessments	Day 1 ±14 Days	Every 6 Months ±14 Days
Physical examination and body weight	X	
Dermatological exam	X	
Vital signs (temperature, blood pressure, pulse rate)[a]	X	
Laboratory tests		
Thyroid function	X	
Urinalysis	X	
Hematology[b]	X	
Blood chemistry[c]	X	
Disease assessment, including CT or MRI scan		X
Creatine kinase		X
12-lead ECG		X
SAE reporting	SAEs will be collected from signing of informed consent form through 30 days after the last dose of study drug[d]	
MLN2480 Q2D administration[e]	Continuous dosing	

a Predose.

b Hematology will be tested at local laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin <9 g/dL, despite blood transfusion), absolute differential, and ANC.

c Blood chemistry results include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

d Including serious pretreatment events; see Section 9.

e Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose.

Pharmacokinetic and Electrocardiogram Sampling Schedule A: Q2D Dose Escalation Phase

Table 1-1 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Q2D Dose Escalation Phase)

Cycle 1, Day 1: • Predose (within 1 hour prior to dose)[a] • 30 minutes postdose (± 5 minutes) • 1 hour postdose (± 10 minutes) • 2 hours postdose (± 30 minutes) • 4 hours postdose (± 30 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes)
Cycle 1, Day 2: • 24 hours post Cycle 1, Day 1 dose (± 1 hour)
Cycle 1, Day 3[b]: • 48 hours post Cycle 1[a], Day 1 dose (predose within 1 hour prior to Cycle 1, Day 3 dose)
Cycle 1, Day 9[b]: • Predose (within 1 hour prior to dose)[a]
Cycle 1, Day 15[b]: • Predose (within 1 hour prior to dose)[a]
Cycle 1, Day 21[b]: • Predose (within 1 hour prior to dose)[a] • 30 minutes postdose (± 5 minutes) • 1 hour postdose (± 10 minutes) • 2 hours postdose (± 30 minutes) • 4 hours postdose (± 30 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes)
Cycle 1, Day 22: • 24 hours post Cycle 1, Day 21 dose (± 1 hour)
Cycle 1, Day 23[b,c]: • 48 hours post Cycle 1, Day 21 dose (predose[a], within 1 hour prior to Cycle 1, Day 23 dose)
Cycle 2, Day 1: • predose, within 1 hour prior to Cycle 2, Day 1 dose[a]

a All predose PK samples should be collected prior to dosing in the clinic.
b Predose samples should be collected at approximately the same time as the morning dosing times on previous days of the cycle. Patients should be instructed to refrain from taking their morning dose before coming to the clinic.
c 28-day cycle only.

Table 1-2 MLN2480 Urine Samples for Pharmacokinetic Assessments (Q2D Dose Escalation Phase)

Cycle 1, Day 1:
• Predose
Cycle 1, Day 21:
• 0-8-hour collection after Cycle 1, Day 21 dose[a]

a The 0-8-hour collection should be completed immediately prior to collection of the 8-hour plasma PK sample.

Table 1-3 MLN2480 Triplicate ECG Assessment Time Points (Q2D Dose Escalation Phase)

Cycle 1, Day 1:
• Predose (within 1 hour prior to dose)
• 2 hours postdose
• 4 hours postdose
• 6 hours postdose
Cycle 1, Day 3:
• 48 hours post Cycle 1, Day 1 dose (predose within 1 hour prior to Cycle 1, Day 3 dose)
Cycle 1, Day 21 :
• Predose (within 1 hour prior to dose)
• 2 hours postdose
• 4 hours postdose
• 6 hours postdose
Cycle 2, Day 1:
• Predose (within 1 hour prior to Cycle 2, Day 1 dose)

Triplicate 12-lead ECG measurements should be performed after a 5-minute rest period in the supine position and will be recorded at 2- to 5-minute intervals immediately before the collection of the corresponding blood PK sample.

Pharmacokinetic and Electrocardiogram Sampling Schedule B: Q2D PK Expansion Cohort (Dose Expansion Phase)

Dosing Q2D C1: D1-D21of a 28-day cycle (D1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21; no dosing D22-D28)

Dosing Q2D C2 and beyond: 28-day cycle (D1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27)

Table 1-4 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Q2D PK Expansion Cohort)

Cycle 1, Day 1: • Predose (within 1 hour prior to dose)[a] • 30 minutes postdose (± 5 minutes) • 1 hour postdose (± 10 minutes) • 2 hours postdose (± 30 minutes) • 4 hours postdose (± 30 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes)
Cycle 1, Day 2: • 24 hours post Cycle 1, Day 1 dose (± 1 hour)
Cycle 1, Day 3[b]: • 48 hours post Cycle 1, Day 1 dose (predose within 1 hour prior to Cycle 1, Day 3 dose)[a]
Cycle 1, Day 9[b]: • Predose (within 1 hour prior to dose)[a]
Cycle 1, Day 15[b]: • Predose (within 1 hour prior to dose)[a]
Cycle 1, Day 21[b]: • Predose (within 1 hour prior to dose)[a] • 30 minutes postdose (± 5 minutes) • 1 hour postdose (± 10 minutes) • 2 hours postdose (± 30 minutes) • 4 hours postdose (± 30 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes)
Cycle 1, Day 22: • 24 hours post Cycle 1, Day 21 dose (± 1 hour)

Table 1-4 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Q2D PK Expansion Cohort)

Cycle 1, Day 23 :
• 48 hours post Cycle 1, Day 21 dose (± 1 hour)
Cycle 1, Day24
• 72 hours post Cycle 1, Day 21 dose (± 2 hours)
Cycle 1, Day 25
• 96 hours post Cycle 1, Day 21 dose (± 4 hours)
Cycle 1, Day 26
• 120 hours post Cycle 1, Day 21 dose (± 6 hours)
Cycle 2, Day 1:
• 192 hours post Cycle 1, Day 21 dose (predose[a], within 1 hour prior to Cycle 2, Day 1 dose)

a All predose PK samples should be collected prior to dosing in the clinic.

b Predose samples should be collected at approximately the same time as the morning dosing times on previous days of the cycle. Patients should be instructed to refrain from taking their morning dose before coming to the clinic.

Table 1-5 MLN2480 Urine Samples for Pharmacokinetic Assessments (Q2D PK Expansion Cohort)

Cycle 1, Day 1:
• Predose
Cycle 1, Day 21:
• 0-8-hour collection post-Cycle 1, Day 21 dose[a]

a The 0-8 hour collection should be completed immediately prior to collection of the 8-hour plasma PK sample.

Table 1-6 MLN2480 Triplicate ECG Assessment Time Points (Q2D PK Expansion Cohort)

Cycle 1, Day 1:
• Predose (within 1 hour prior to dose)
• 2 hours postdose
• 4 hours postdose
• 6 hours postdose
Cycle 1, Day 3:
• 48 hours post Cycle 1, Day 1 dose (predose within 1 hour prior to Cycle 1, Day 3 dose)
Cycle 1, Day 21 :
• Predose (within 1 hour prior to dose)
• 2 hours postdose
• 4 hours postdose

Table 1-6 MLN2480 Triplicate ECG Assessment Time Points (Q2D PK Expansion Cohort)

• 6 hours postdose
Cycle 1, Day 23
• 48 hours post-Cycle 1, Day 21 dose
Cycle 1, Day 25
• 96 hours post-Cycle 1, Day 21 dose
Cycle 2, Day 1:
• 192 hours post-Cycle 1, Day 21 dose (pre-Cycle 2, Day 1 dose)

Triplicate 12-lead ECG measurements should be performed after a 5-minute rest period in the supine position and will be recorded at 2- to 5-minute intervals immediately before the collection of the corresponding blood PK sample.

Pharmacokinetic and Electrocardiogram Sampling Schedule C: Q2D Melanoma Expansion Cohorts (Dose Expansion Phase)

Dosing: Q2D, 28-day cycle (D1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27)

Table 1-7 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Melanoma Expansion Cohorts)

Cycle 1, Day 1:
• Predose (within 1 hour prior to dose)[a]
• 2 to 4 hours postdose
Cycle 1, Day 9[b]**:**
• Predose (within 1 hour prior to dose)[a]
Cycle 1, Day 21[b]**:**
• Predose (within 1 hour prior to dose)[a]
• 2 to 4 hours postdose
Cycle 1, Day 22:
• 22 to 30 hours post Cycle 1, Day 21 dose
Cycle 2, Day 1:
• Predose (within 1 hour prior to dose)[a]
• 2 to 4 hours postdose

a All predose PK samples should be collected prior to dosing in the clinic.
b Samples should be collected at approximately the same time as the morning dosing times on previous days of the cycle. Patients should be instructed to refrain from taking their morning dose before coming to the clinic.

Note: No urine PK or triplicate ECG assessments will be done in the Q2D melanoma expansion cohorts.

Pharmacokinetic and Electrocardiogram Sampling Schedule D: QW Dose Escalation and Dose Expansion Phases

Dosing: QW, 28-day cycle (D1, 8, 15, 22)

Table 1-8 MLN2480 Plasma Pharmacokinetic Assessment Time Points (QW Dose Escalation and Dose Expansion Phase)

Cycle 1, Day 1: • Predose (within 1 hour prior to dose)[a] • 1 hour postdose (± 10 minutes) • 2 hours postdose (± 15 minutes) • 3 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 5 hours postdose (± 15 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes)
Cycle 1, Day 2: • 24 hours post Cycle 1, Day 1 dose (± 1 hour)
Cycle 1, Day 3: • 48 hours post Cycle 1[a], Day 1 dose (± 4 hours)
Cycle 1, Day 6: • 120 hours post Cycle 1, Day 1 dose (± 24 hours)
Cycle 1, Day 8: • Predose (within 1 hour prior to dose)[a]
Cycle 1, Day 15: • Predose (within 1 hour prior to dose)[a]
Cycle 1, Day 22[b]: • Predose (within 1 hour prior to dose)[a] • 1 hour postdose (± 10 minutes) • 2 hours postdose (± 15 minutes) • 3 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 5 hours postdose (± 15 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes)
Cycle 1, Day 23: • 24 hours post Cycle 1, Day 22 dose (± 1 hour)

Table 1-8 MLN2480 Plasma Pharmacokinetic Assessment Time Points (QW Dose Escalation and Dose Expansion Phase)

Cycle 1, Day 24 [b]**:**
• 48 hours post Cycle 1, Day 22 dose (± 4 hours)
Cycle 1, Day 27:
• 120 hours post Cycle 1, Day 22 dose (± 24 hours)
Cycle 2, Day 1:
• Predose (within 1 hour prior to dose)[a]

a All predose PK samples should be collected prior to dosing in the clinic. Predose samples should be collected at approximately the same time as the morning dosing times on previous days of the cycle.
b Patients should be instructed to refrain from taking their morning dose before coming to the clinic.

Pharmacokinetic and Electrocardiogram Sampling Schedule E: Alternative (Split Dose, Same Day) QW Dose Escalation and Dose Expansion Phases

Dosing: QW with BID dosing on Day 1, 8, 15, and 22 in the 28-day cycle

Table 1-9 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Alternative QW1 Dose Escalation and Expansion Phase)

Cycle 1, Day 1:
• Predose (within 1 hour prior to AM dose)[a]
• 1 hour postdose (± 10 minutes)
• 2 hours postdose (± 15 minutes)
• 3 hours postdose (± 15 minutes)
• 4 hours postdose (± 15 minutes)
• 5 hours postdose (± 15 minutes)
• 6 hours postdose (± 30 minutes)
• 8 hours postdose (± 45 minutes)
• 12 hours post dose (± 60 minutes, prior to PM dose)
Cycle 1, Day 8 :
• Predose (within 1 hour prior to AM dose) [a]
Cycle 1, Day 15 :
• Predose (within 1 hour prior to AM dose) [a]
Cycle 1, Day 22 [b]**:**
• Predose (within 1 hour prior to AM dose)[a]
• 1 hour postdose (± 10 minutes)
• 2 hours postdose (± 15 minutes)
• 3 hours postdose (± 15 minutes)
• 4 hours postdose (± 15 minutes)

Table 1-9 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Alternative QW1 Dose Escalation and Expansion Phase)

• 5 hours postdose (± 15 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes) • 12 hours postdose (± 60 minutes prior to PM dose)
Cycle 1, Day 23: • 24 hours post Cycle 1, Day 22 AM dose (± 1 hour)
Cycle 1, Day 24: • 48 hours post Cycle 1, Day 22 AM dose (± 4 hours)
Cycle 1, Day 27: • 120 hours post Cycle 1, Day 22 AM dose (± 24 hours)
Cycle 2, Day 1: • Predose (within 1 hour prior to AM dose)[a,b]

a All predose PK samples should be collected prior to dosing in the clinic. Predose samples should be collected at approximately the same time as the morning dosing times on previous days of the cycle.
b Patients should be instructed to refrain from taking their morning dose before coming to the clinic.

Pharmacokinetic and Electrocardiogram Sampling Schedule F: Alternative (Split Dose, Sequential Days) QW Dose Escalation and Dose Expansion Phases

Dosing: QW with dosing on Days 1 & 2, Days 8 & 9, Days 15 & 16 and Days 22 & 23 in the 28-day cycle

Table 1-10 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Alternative QW2 Dose Escalation and Expansion Phase)

Cycle 1, Day 1: • Predose (within 1 hour prior to dose)[a] • 2 hours postdose (± 15 minutes) • 3 hours postdose (± 15 minutes) • 6 hours postdose (± 30 minutes)
Cycle 1, Day 2: • Predose (~ 24 hr post D1 dose, prior to D2 dose) • 1 hour postdose (± 10 min) • 2 hour postdose (± 15 min) • 3 hour postdose (± 15 min) • 4 hour postdose (± 15 min) • 5 hour postdose (± 15 min) • 6 hour postdose (± 30 min) • 8 hour postdose (± 30 min)

Table 1-10 MLN2480 Plasma Pharmacokinetic Assessment Time Points (Alternative QW2 Dose Escalation and Expansion Phase)

Cycle 1, Day 3: • 24 hours post Cycle 1, Day 2 dose (± 4 hours)
Cycle 1, Day 4: • 48 hours post Cycle 1, Day 2 dose (± 4 hours)
Cycle 1, Day 7: • 120 hours post Cycle 1, Day 2 dose (± 24 hours)
Cycle 1, Day 8 : • Predose (within 1 hour prior to dose) [a]
Cycle 1, Day 15 : • Predose (within 1 hour prior to dose) [a]
Cycle 1, Day 22 [b]: • Predose (within 1 hour prior to dose)[a] • 2 hours postdose (± 15 minutes) • 3 hours postdose (± 15 minutes) • 6 hours postdose (± 30 minutes)
Cycle 1, Day 23: • Predose (within 1 hour prior to dose)[a] • 1 hour postdose (± 10 minutes) • 2 hours postdose (± 15 minutes) • 3 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 5 hours postdose (± 15 minutes) • 6 hours postdose (± 30 minutes) • 8 hours postdose (± 45 minutes)
Cycle 1, Day 24: • 24 hours post Cycle 1, Day 23 dose (± 4 hours)
Cycle 1, Day 25 • 48 hours post Cycle 1, Day 23 dose (± 4 hours)
Cycle 1, Day 28: • 120 hours post Cycle 1, Day 23 dose (± 24 hours)
Cycle 2, Day 1: • Predose (within 1 hour prior to dose)[a]

a All predose PK samples should be collected prior to dosing in the clinic. Predose samples should be collected at approximately the same time as the morning dosing times on previous days of the cycle.

b Patients should be instructed to refrain from taking their morning dose before coming to the clinic.

Table 1-11 MLN2480 Urine Samples for Pharmacokinetic Assessments (QW and Alternative QW Dose Escalation Phase)

Cycle 1, Day 1:
• Predose
Cycle 1, Day 22 (QW and Alternative QW1):
• 0-8-hour collection after Cycle 1, Day 22 dose[a]
Cycle 1, Day 23 (only for Alternative QW2 cohorts)
• 0-8-hour collection after Cycle 1, Day 23 dose[a]

a The 0-8 hour urine collection should be completed immediately prior to collection of the 8-hour plasma PK sample.

Table 1-12 MLN2480 Triplicate ECG Assessment Time Points (QW and Alternative QW Dose Escalation Phase)

Cycle 1, Day 1:
• Predose (within 1 hour prior to dose)
• 2 hours postdose
• 3 hours postdose
• 4 hours postdose
• 5 hours postdose
• 6 hours postdose
Cycle 1, Day 22[a] :
• Predose (within 1 hour prior to dose)
• 2 hours postdose
• 3 hours postdose
• 4 hours postdose
• 5 hours postdose
• 6 hours postdose

Triplicate 12-lead ECG measurements should be performed after a 5-minute rest period in the supine position and will be recorded at 2- to 5-minute intervals immediately before the collection of the corresponding blood PK sample.

a For Alternative QW2 dosing schedule, the triplicate ECG assessment will be performed on Cycle 1 Day 23.

Note: No urine PK or triplicate ECG assessments will be done in the QW dose expansion cohorts.

Tumor Tissue Samples for Pharmacodynamic and Correlative Biomarker Analysis: Q2D and QW (Including Alternative QW Schedules)

Required Tissue Sample

CCI

[redacted]

Optional Tissue Sample

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BID	*bis in die*; twice daily
CL_r	renal clearance
C_{max}	maximum plasma concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
C_{trough}	trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DOR	duration of response
DTIC	dacarbazine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ERK	extracellular signal-regulated kinase
EU	European Union
FDA	United States Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HNSTD	highest nonseverely toxic dose
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL	interleukin
IRB	institutional review board
mAbs	monoclonal antibodies
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MEK	MAPK or extracellular signal-regulated kinase
MET	mesenchymal-epithelial transition factor
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NPO	nothing by mouth
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
pERK	phosphorylated extracellular signal-regulated kinase
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
QD	*quaque die*; each day; once daily
Q2D	every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	weekly dosing
RDC	remote data capture
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TAK-580	New product code for MLN2480
TEAE	treatment-emergent adverse event
T_{max}	first time to maximum plasma concentration
ULN	upper limit of the normal range
US	United States

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

MLN2480, currently known as TAK-580, is a potent, small molecule pan-RAF kinase inhibitor being developed for the treatment of solid tumors, including locally advanced, metastatic, and/or unresectable melanoma. The RAF kinases (A-RAF, B-RAF, and C-RAF) are key components of the mitogen-activated protein kinase (MAPK) pathway that controls cell proliferation and survival signaling.[1,2] The MAPK pathway, which is composed of RAS, RAF, MAPK or extracellular signal-regulated kinase 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, mesenchymal-epithelial transition factor (MET), and vascular endothelial growth factor receptor.[3] Genetic alterations in the MAPK pathway are among the most common in human cancers. Up to 60% of melanomas harbor *B-RAF* mutations[4] and *K-RAS* mutations have been estimated in roughly 60%, 30%, and 15% of pancreatic, colon, and lung tumors, respectively.[5] B-RAF mutations are also found in 40% of papillary or anaplastic thyroid cancers[6] and in a small percentage of several other types of tumor.[5] A majority of reported B-RAF mutations are a substitution of glutamic acid for valine at the amino acid position of 600 (the V600E mutation). The B-RAF V600E mutation constitutively activates B-RAF and downstream signal transduction in the MAPK pathway.[4]

To address these RAF pathway-driven cancers, small molecule RAF kinase inhibitors have been developed and are currently under clinical investigation or commercially available. In cells carrying the *B-RAF* V600E mutation, RAF compounds inhibit signaling through MEK and ERK, resulting in the expected anti-proliferative effects. PLX4032 (vemurafenib, Plexxikon in collaboration with Roche Pharmaceuticals [Roche ID RG7204]) is a potent inhibitor of *B-RAF* V600E. Nonclinical studies showed that PLX4032 and its analog PLX4720 inhibit the kinase activity of *B-RAF* V600E at low nanomolar concentrations, abrogate signaling through the MAPK pathway, and block proliferation of cells carrying the *B-RAF* V600E mutation in vitro at high nanomolar concentrations.[7,8] Orally administered PLX4032 inhibits the growth and, at higher doses, induces the regression of human melanoma tumors transplanted into immunocompromised mice. The results of this completed phase 1 study were published recently. Of the patients receiving doses of 240 mg or more twice daily (BID) in the dose escalation cohort, 16 had melanoma tumors with the *B-RAF* V600E mutation. Among these 16 patients, the overall response rate (ORR) was 69%

(11 of 16 patients), with 10 partial responses (PRs) and 1 complete response (CR). Among 32 patients with the *B-RAF* V600E mutation in the expansion cohort, 24 had a PR and 2 had a CR.[9] PLX4032 was also investigated in a single-arm phase 2 study evaluating best ORR in 132 previously treated patients with *B-RAF* V600E metastatic melanoma. Preliminary results indicate a confirmed response rate of 52%, including 3 confirmed CRs (no evidence of disease) and 66 confirmed PRs (tumor shrinkage of at least 30%).[10] A recent phase 3 randomized trial has demonstrated that previously untreated *B-RAF* V600E mutation-positive melanoma patients treated with PLX4032 had an improved overall survival (OS) compared to those treated with a standard-of-care agent, dacarbazine (DTIC).[11] Clinical activity was also observed in the first-in-human (FIH) study for the pan-RAF inhibitor XL281, with a clinical benefit rate of 43%, including a confirmed PR in an ocular melanoma patient.[12]

Melanocytes rely on the MAPK and cyclic adenosine monophosphate signaling pathways to maintain the balance between proliferation and differentiation that is critical for normal function.[13] In normal melanocytes, B-RAF alone is responsible for MEK activation, but upon oncogenic activation of RAS, cells switch their signaling dependency from B-RAF to C-RAF.[14] Recently published data using RAS mutant preclinical models has highlighted significant differences in the action of pan-RAF and B-RAF specific inhibitors that may be critical for their clinical application in the treatment of RAS mutant cancers.[15,16] The inhibition of B-RAF by B-RAF specific inhibitors such as PLX4032 induced strong binding of B-RAF to C-RAF in N-RAS mutant melanoma and K-RAS mutant colorectal cancer cell lines, resulting in C-RAF phosphorylation and activation. These observations may indicate that in the presence of activating RAS mutations, B-RAF selective inhibitors are involved in the activation of MEK signaling in a C-RAF-dependent fashion. Although pan-RAF inhibitors are involved in B-RAF and C-RAF heterodimerization in these RAS mutant models, they also inhibit signaling for the heterodimer.[16] Therefore, this differentiation could be relevant not only in the treatment of RAS mutant tumors, but also in the management of B-RAF mutant tumors that become resistant to B-RAF selective inhibition through activation of RAS.[17] Taken together, MLN2480 has a broad therapeutic potential in the treatment of melanoma and other B-RAF and RAS mutant tumors.

1.1.1 Disease Under Treatment

Overview of Melanoma

The incidence of melanoma varies considerably with geography, as would be expected since sun exposure (both the intensity of individual episodes of sun exposure and cumulative

ultraviolet light exposure) is the dominant etiologic risk factor. The publication Cancer Incidence in Five Continents by the International Agency for Research on Cancer volume IX covers the period from 1998 to 2002 and states that the highest recorded incidence of melanoma worldwide is in Queensland, Australia, at a figure of 55.8/100,000/annum for males and 41.1/100,000/annum for females.[18,19] The Surveillance, Epidemiology, and End Results data for the United States (US) lists a melanoma incidence in non-Hispanic whites of 19.4 and 14.4 per 100,000/annum in males and females, respectively. Reported melanoma incidence rates vary for Europe and are highest in Switzerland (16.6 and 19.6 per 100,000/annum in males and females, respectively) and the Scandinavian countries of Norway, Sweden, and Denmark (11.9 to 14.2 and 12.1 to 14.6 per 100,000/annum in males and females, respectively).[19] Data from the majority of countries show that at a time when the incidence of many tumor types is decreasing, melanoma incidence continues to increase.

Approximately 80% of cutaneous melanoma lesions are diagnosed as Stage I tumors, conferring a 90% 5-year survival rate when treated with surgery with or without adjuvant interferon. However, once malignant melanoma becomes metastatic and beyond the scope of surgical resection, it represents one of the most treatment-refractory malignancies.

Current Therapies for Metastatic Melanoma

In metastatic melanoma, single-agent chemotherapeutic agents, including DTIC and temozolomide, produce responses in 10% to 20% of patients, with a median survival of approximately 9 months and a 2-year survival rate of 13%.[20] Response rates for the biologic therapies interferon and interleukin (IL)-2 are also in the range of 10% to 20%. Therefore, none of these therapies appear superior to best supportive care and provide benefit to a majority of patients. Combination chemotherapy regimens, including cisplatin-vinblastine-DTIC and cisplatin-DTIC-carmustine-tamoxifen (Dartmouth regimen), result in improved response rates of 30% to 50%. However, these superior response rates fail to translate into an improvement in median survival and the negative impact on tolerability is significant.[21]

A variety of therapeutic approaches have reached late-stage development or have been approved for treatment of metastatic melanoma,[22] including the immunomodulatory antibody ipilimumab,[23] vermurafenib (PLX-0432), dabrafenib, and trametinib.

Ipilimumab was approved based on a three-armed phase 3 study (MDX010-20); ipilimumab and gp100 (an experimental melanoma vaccine) in combination, versus ipilumimab and gp100 placebo in combination, versus ipilimumab placebo and gp100 in combination. The

median overall survival for ipilimumab was 10.1 months compared with 6.4 months for gp100; the investigator-assessed objective response rate was 10.9% in the ipilimumab arm and 1.5% in the gp100 arm.[24] The safety profile showed that ipilimumab was most commonly associated with AEs resulting from increased or excessive immune activity. These immune-related AEs (irAEs) primarily involved the gastrointestinal (GI) tract and skin, and less frequently, the liver, endocrine glands, and nervous system. While most irAEs occurred during the induction period, onset has also been reported months after the last dose of ipilimumab, making monitoring of these events challenging.[25]

The results of another phase 3 study comparing ipilimumab and DTIC in combination against DTIC alone in patients with previously untreated metastatic melanoma have been published.[26] Overall survival was significantly longer in the group receiving ipilimumab and DTIC than in the group receiving DTIC alone (11.2 and 9.1 months, respectively). However, Grade 3 or 4 adverse events (AEs) occurred in 56.3% of patients treated with ipilimumab and DTIC, as compared with 27.5% treated with DTIC alone.

The oral targeted therapy vemurafenib (PLX-4032) was additionally approved for patients with melanoma whose tumors have the BRAF V600E mutation. The phase 3 trial demonstrated an OS advantage over DTIC.[11] However, roughly one half of patients enrolled in PLX-4032 vemurafenib clinical studies eventually progressed, indicating that acquired resistance may impact long-term clinical activity[27] and one of resistance mechanisms has been demonstrated as activation of RAS.[17,28]

Most recently approved for patients with BRAF V600E positive melanoma are dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor). Both drugs significantly improved the median progression-free survival compared with chemotherapy in phase 3 studies. However, as is the case with vemurafenib, these responses are considered short-lived.[30] Ongoing trials examine the use of these 2 drugs in combination.[29,30]

Other therapies, including anti-PD-1 and anti-PDL-1 monoclonal antibodies (mAbs) and a variety of signaling pathway inhibitors, are currently in various stages of clinical development.[31,32] Given the rapid rise in the incidence of melanoma and the limited options for effective treatment of metastatic melanoma as well as resistance developed in patients treated with vemurafenib and high incidence of AEs with ipilimumab, the evaluation of different treatment strategies, including targeted therapies such as pan-RAF inhibitors to overcome these clinical challenges, is warranted.

1.1.2 Study Drug

MLN2480 is a potent, small-molecule, pan-RAF kinase inhibitor being developed for the treatment of solid tumors, including locally advanced, metastatic, and/or unresectable melanoma.

1.2 Nonclinical Experience

Pharmacology

Nonclinical studies support the potential therapeutic benefits of MLN2480 in solid tumors, including metastatic melanoma and colon cancer. MLN2480 was tested in a variety of in vitro biochemical and cell-based assays to measure its potency, selectivity, and activity in cancer cell lines. In biochemical kinase inhibition assays, MLN2480 potently inhibited each RAF kinase isoform tested: B-RAF V600E mutant, B-RAF wild-type, and C-RAF wild-type. To gage its selectivity, MLN2480 was screened on a large panel of human kinases and non-kinase targets and showed a high degree of selectivity for RAF kinases. To determine the activity of MLN2480 on cancer cells, MLN2480 was tested in a panel of 42 cancer cell lines from a variety of different tumor types and with different genetic mutations for its antiproliferative activity. Inhibition of phosphorylated ERK (pERK) signaling was measured in a subset of 23 of these cell lines to correlate inhibition of RAF signaling with antiproliferative activity. These cancer cell lines exhibited a range of sensitivities to MLN2480, with the B-RAF mutant cell lines being the most sensitive. A subset of the B-RAF wild-type cell lines, including the RAS mutant cell lines, was also sensitive. To assess the in vivo potency and pan-RAF activity of MLN2480, several tumor pharmacodynamic studies were conducted. In these studies, tumor-bearing mice were administered a single oral dose of MLN2480 and the degree of pERK suppression was measured at different time points, along with plasma and tumor drug levels to assess the pharmacokinetic (PK)/pharmacodynamic correlation. MLN2480 showed strong and sustained suppression of the pERK biomarker in both B-RAF mutant and wild-type tumor xenograft models, indicating that MLN2480 is a potent pan-RAF inhibitor in vivo. The in vivo antitumor activity of MLN2480 was evaluated by testing MLN2480 in 12 different tumor xenograft models with oral dosing on an every other day (Q2D) or once daily (QD) schedule. The tumor models tested included melanoma, colon, lung, pancreatic, and prostate cancer models that differed in their B-RAF mutation and RAS mutation status. MLN2480 showed significant antitumor activity in 9 of these 12 models on the QD schedule, including models of melanoma, colon, lung, and pancreatic cancer. The 9 models in which MLN2480 showed significant antitumor activity included 4 B-RAF mutant and 5 B-RAF wild-type

models, consistent with the in vivo pan-RAF activity of MLN2480. B-RAF mutant tumor models were the most sensitive to MLN2480 with regressions of large, established tumors observed in 2 melanoma models: WM-266-4 *B-RAF*V600D and A-375 *B-RAF*V600E. On the Q2D schedule, MLN2480 was efficacious at several doses in the 2 models where this schedule was tested, the WM-266-4 melanoma B-RAF mutant model and the Colo-205 B-RAF mutant model. The efficacy of MLN2480 was also evaluated in combination with several oncology therapeutics in some of these tumor models, including oxaliplatin, irinotecan, bevacizumab, carboplatin, and gemcitabine. These combination data may support clinical testing of MLN2480 following the initial phase 1 study.

Pharmacokinetics

Nonclinical studies were conducted to evaluate PK characteristics of MLN2480. Results indicated that MLN2480 was well absorbed after oral administration and was cleared slowly, demonstrating a relatively long plasma elimination half-life ($t_{1/2}$). Apparent volumes of distribution estimates suggest that MLN2480 is distributed to peripheral tissues. Every other day dosing in rats and monkeys did not result in notable MLN2480 accumulation.

In vitro studies indicated that MLN2480 was not a potent, reversible inhibitor of cytochrome P_{450} (CYP) 1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. The concentration producing 50% inhibition (IC_{50}) values were > 100μM for CYP1A2, CYP2B6, CYP2D6, CYP2E1, and CYP3A4 (midazolam). The IC_{50} values for CYP2C9, CYP2C19, and CYP3A4 (testosterone) were 46.5, 82.8, and 40.5 μM, respectively. In addition, no time-dependent inhibition of CYP3A4 was observed. Studies in human hepatocytes indicated that MLN2480 is not an inducer of CYP1A2 and CYP2C9 and suggested a low potential for CYP3A4, CYP2B6, and CYP2C19 induction. Overall, these results suggest there is a low probability for MLN2480 to cause drug-drug interactions via CYP induction, or via inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.

In contrast to the above enzymes, MLN2480 reversibly inhibited CYP2C8 with an IC_{50} of 7.8 μM. When considered in the context of MLN2480 exposures, it is inferred that there is a potential risk for MLN2480 administration to result in increased exposures of co-administered agents that are predominantly metabolized by CYP2C8 due to inhibition of this enzyme. Therefore, co-administration of CYP2C8 substrates with MLN2480 should be used with caution.

In vitro data indicates that MLN2480 is metabolized by aldehyde oxidase and CYPs 2C8, 2C9, 2C19, and 3A4, with relative contributions of 49%, 33%, 8%, 7%, and 4%, respectively. Based on this data, concomitant use of strong and moderate inducers of CYP3A and CYP2C enzymes, and strong inhibitors of CYP2C8, is prohibited during the study.

Toxicology

Non-Good Laboratory Practice (GLP), 14-day, pilot, repeat-dose tolerability studies of MLN2480 in rats (0, 50, 150, 500, and 1,000 mg/kg) and monkeys (0, 3, 10, and 30 mg/kg) were performed to evaluate MLN2480 administered orally QD. Accumulation of MLN2480 was observed with daily dosing. MLN2480 was well tolerated in male rats at up to 1,000 mg/kg QD and in female rats at 50 or 150 mg/kg QD orally for 14 days. Several female rats and several monkeys were sacrificed in moribund condition after 7 or more doses. Target organ toxicity in female rats at 150 and 500 mg/kg QD included the ovaries (presence of corpora hemorrhagicum and/or hemorrhage), vagina (increased thickness of the vaginal mucosa), and skin (ulceration and accumulation of neutrophils along the epidermis). Additional target organs at 500 mg/kg QD in female rats included the thymus (lymphocyte necrosis in the thymic cortex, occasional mineralized blood vessels [predominately in the medulla] and thinning of the cortex), small intestine (increased frequency of crypt microabscesses), and lymph nodes (erythrophagocytosis, hemorrhage, and/or lymphocyte necrosis in 1 or more lymph nodes). In monkeys, target organs in moribund and non-moribund animals at all doses included the bone marrow (hypercellularity in myeloid lines and hypocellularity of the erythroid lines), thymus (lymphoid depletion), and gastrointestinal tract (infiltration of mixed cells in the lumen and mucosa). Cause of death was not determined in this study.

With less frequent repeat dosing compared to QD, non-GLP and GLP toxicology studies showed that MLN2480 was better tolerated (no mortality) in nonclinical species and showed no evidence of persistent MLN2480 accumulation. In 4-week, Q2D, repeat-dose, GLP studies, the target organ of toxicity common to both monkey (0, 3, 10, and 30 mg/kg) and rat (0, 50, 150, and 500 mg/kg) was bone marrow (focal precursor depletion in rat and erythroid hypocellularity in monkey). Additionally, decreases in mean red blood cells, hemoglobin, hematocrit, and absolute reticulocyte counts, and increases in serum transaminases were observed in both species. Target organs of toxicity specific to rats included the duodenum (crypt microabscesses), ileum (crypt ectasia), ovaries (increased size and/or numbers of corpora hemorrhagicum and/or hemorrhage), and vagina (increased thickness of the vaginal

mucosa). The relevance of the ovarian and vaginal findings to humans is unclear, as the estrus cycle and pathways for luteolysis differ between rodents and humans. However, these findings were not observed in monkeys. Increases in serum bilirubin and decreases in mean white blood cells were also noted in rats. Target organs of toxicity specific to monkeys included thymus (decreases in the thickness of the thymic cortex and medulla), thyroid (decreases in the size and numbers of follicles, fibrosis and occasional mononuclear cell infiltrates and hemorrhage), and large intestine (mixed cell infiltrates in the mucosa and occasional accumulations of neutrophils and necrotic debris in the lumen and crypts). Increases in mean white blood cells and absolute neutrophil counts were also monkey-specific, as well as decreases in serum albumin with associated decreases in the albumin:globulin ratio, serum calcium, and serum phosphorous and associated increases in parathyroid hormone. The majority of findings were completely reversible, with the only exceptions being ovarian findings in rats and thymus changes in monkeys.

Safety pharmacology and genotoxicology studies indicated that MLN2480 is not mutagenic or clastogenic, and that MLN2480 has a low risk for central nervous system, respiratory, and cardiovascular liabilities.

Please refer to the Investigator's Brochure (IB) for more details on these nonclinical studies.

1.3 Clinical Experience

This study is the first evaluation of MLN2480 in humans; therefore, no previous human experience is available.

1.4 Study Rationale

Given the rapid rise in the incidence of melanoma and the limited options for effective treatment of metastatic melanoma, a pan-RAF inhibitor like MLN2480 that produces MAPK blockade at the level of RAF could provide clinical benefit and unmet medical need in patients with locally advanced, metastatic, and/or unresectable melanoma. This FIH study will be conducted in 2 phases. The Dose Escalation phase will evaluate the safety profile and determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of MLN2480, taken as monotherapy by patients with advanced relapsed or refractory solid tumors. Two dosing schedules of Q2D and QW will be tested to further determine the optimal dosing regimen for MLN2480.

Once the MTD and/or RP2D has been identified for the 28-day treatment cycle, the Dose Expansion phase will commence at that dose level in patients with locally advanced,

metastatic, and/or unresectable melanoma (Q2D Cohorts 1-6 and QW Cohort 9), or in patients with advanced solid tumors, excluding lymphoma, but including melanoma (Q2D Cohort 7). The Dose Expansion phase may commence before establishing the MTD/RP2D upon medical determination of a safe dose that is lower than MTD/RP2D. Tumor genotype is likely to serve as a predictor of response for patients with melanoma, and patients in dose expansion will be assigned to 1 of 8 cohorts based on tumor genotype and treatment history. Safety and preliminary antitumor activity of MLN2480 will be further characterized in patients in the dose expansion cohorts.

Cohort 7 in the Q2D Dose Expansion phase, the PK Expansion cohort, will include patients with any advanced solid tumor (excluding lymphoma, but including melanoma) who have failed or are not candidates for standard therapies or for whom no approved therapy is available. In addition to contributing to the evaluation of safety, tolerability, and preliminary antitumor activity, the PK Expansion cohort will be used to more fully characterize MLN2480 PK including half-life.

1.5 Rationale for Dose and Schedule Selection

A sustained, high degree of target suppression in tumor tissue has been reported to be necessary for maximal activity with RAF and MEK inhibitors, both in nonclinical models and in the PLX4032 phase 1 clinical study.[27,33-35] In mouse tumor pharmacodynamic models, MLN2480 caused strong and sustained suppression of the pERK biomarker at a dose of 50 mg/kg (> 80% suppression for > 16 hours following a single, oral dose), which also demonstrated antitumor activity in multiple tumor xenograft models, on both QD and Q2D dosing schedules. This strong and sustained inhibition of RAF is expected to translate to the clinical setting, since the $t_{1/2}$ of MLN2480 in humans is greater than 24 hours, which is significantly longer than that in mice (approximately 8 hours). Therefore, it is anticipated that administering MLN2480 on a Q2D schedule will provide the required degree of target inhibition over the 48-hour dosing interval.

In nonclinical studies, MLN2480 Q2D dosing was better tolerated than QD dosing in monkeys. Therefore, MLN2480 Q2D dosing is expected to provide an acceptable tolerability profile in humans, while still providing efficacious MLN2480 exposures. The MLN2480 starting dose of 20 mg is equivalent to one-sixth of the highest non-severely toxic dose (HNSTD)[36] established in GLP monkey toxicology studies and corrected for differences in MLN2480 exposures between GLP monkey toxicology studies (using

polyethylene glycol as vehicle) and monkey pharmacokinetic studies using the FIH clinical formulation (tablet).

The magnitude of individual dose escalation increments and the specifics of the dose escalation design are based on the observed toxicities in the monkey (the most sensitive toxicology species), the estimated safety margins with respect to the HNSTD at each human dose, and the likely effective dose range in humans (calculated to be > 160 mg for MLN2480).

Amendment 3 redefines the study cycle length from 22 days (11 doses) to 28 days (14 doses) to improve clinical feasibility and better facilitate future combination with other drugs. Upon implementation of Amendment 3, any ongoing dose escalation cohort will continue enrollment on the 22-day cycle schedule until the cohort is full and all patients have been evaluated for dose-limiting toxicity (DLT) (see Section 6.2). For all subsequent dose escalation cohorts and all dose expansion cohorts, patients will be treated Q2D on a 28-day cycle (14 doses). Patients who began treatment on the 22-day cycle will remain on the original treatment schedule for the duration of their participation in the study.

For the Q2D dosing schedule, regardless of cycle length, dosing is every other day, on a continuous basis, with no treatment-free period between cycles (except for cycle 1 in the PK Expansion cohort). Administration of the same unit dose every other day in a 28-day cycle instead of a 22-day cycle represents a 27% increase in total cycle dose, which is less than the smallest (33%) increase in total cycle dose originally planned for the 22-day cycle in the Dose Escalation phase. After tolerability is confirmed when the same unit dose is administered every other day in a 28-day cycle instead of a 22-day cycle, subsequent dose escalations in a 28-day cycle will consist of a 33% increase in both unit and total cycle dose.

The rationale for evaluation of weekly dosing as an alternate dosing schedule is as follows: Analysis of exposure-efficacy relationships in preclinical mouse xenograft models of tumor growth inhibition indicate that more robust MAP kinase pathway inhibition may be required for antitumor activity in NRAS/ KRAS mutant tumors when compared to BRAF mutant tumors. A weekly dosing schedule can therefore be expected to achieve higher unit doses, which may allow achievement of higher MLN2480 concentrations, and therefore a higher degree of pathway inhibition for a window of time within the dosing interval, without compromising overall dose density. The starting dose of the QW schedule is 400 mg, which is approximately 43% increase from the maximum administered unit dose of 280 mg Q2D.

However, the total cycle dose density for 400 mg QW is 43% lower than that of the current MTD of MLN2480 at 200 mg Q2D.

In addition, AEs observed to date in the first week of treatment at doses up to 280 mg Q2D that were considered to be drug related were generally mild in nature. One case of each of the following was observed within the first week of Q2D treatment (4 doses):

- Grade 2 intermittent fatigue (onset on Day 2)
- Grade 1 intermittent constipation (onset on Day 3)
- Grade 3 diarrhea (onset Day 5)
- Grade 2 intermittent myalgia (onset on Day 5)
- Grade 1 chills (onset on Day 6)
- Grade 1 intermittent arthralgia (onset on Day 7)

The Grade 3 event of diarrhea, which was reported in a patient in the 280 mg Dose Escalation cohort, resolved in 2 days. These data, taken together, support the starting dose of 400 mg QW.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of the study are as follows:

- To evaluate the safety and tolerability of MLN2480 taken orally Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation and Dose Expansion phase and PK Expansion cohort) or locally advanced, metastatic, and/or unresectable melanoma (Dose Expansion phase)
- To determine the MTD of MLN2480 taken Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation phase)
- To determine the recommended phase 2 dose (RP2D) of MLN2480 taken Q2D or QW by patients with relapsed or refractory solid tumors (Dose Escalation phase)

2.2 Secondary Objectives

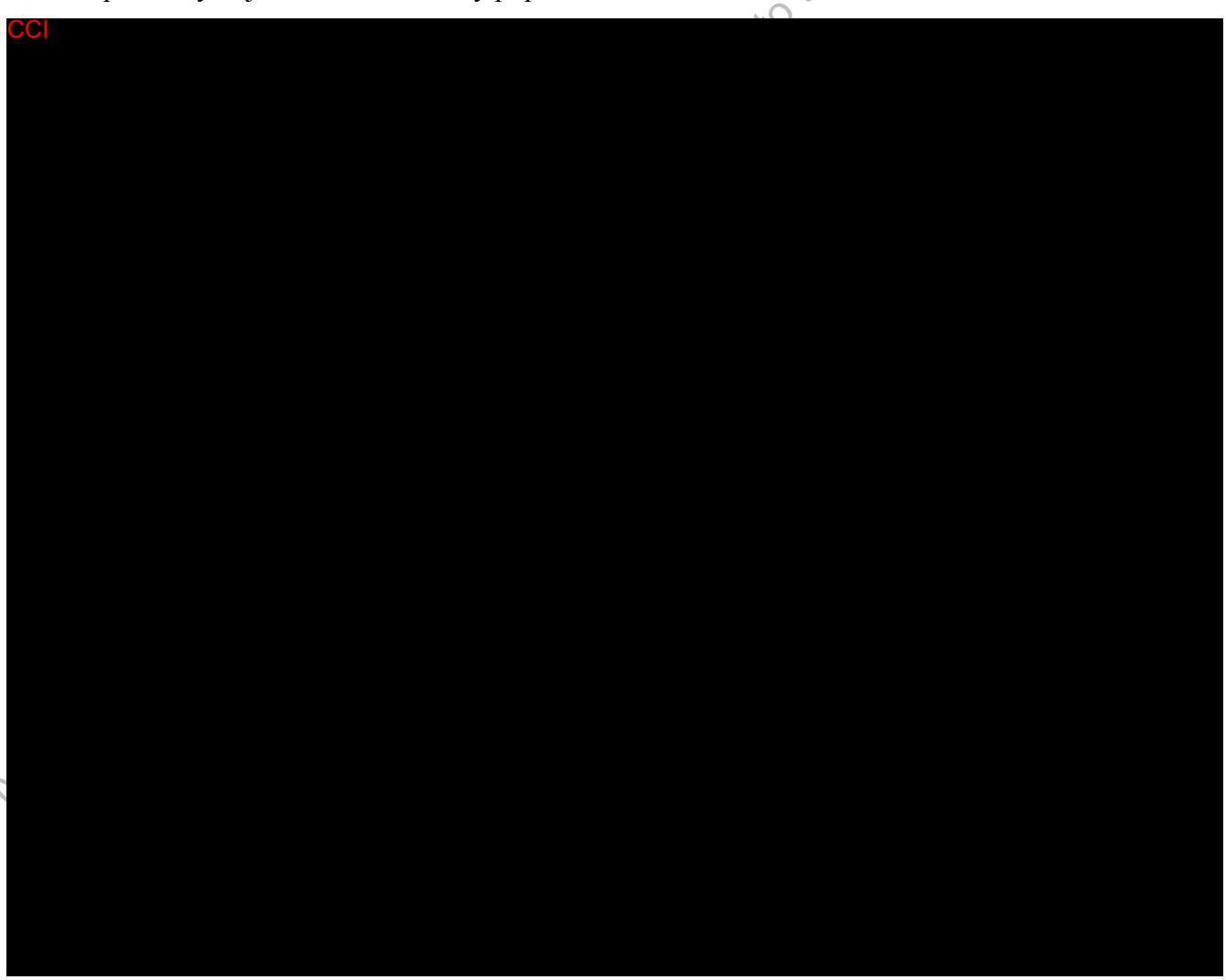
The secondary objectives in this study population are as follows:

- To evaluate the preliminary efficacy of MLN2480 as measured by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1
- To evaluate the pharmacokinetics of MLN2480
- To evaluate the effect of MLN2480 on pharmacodynamic markers in paired tumor biopsies

2.3 Exploratory Objectives

The exploratory objectives in this study population are as follows:

CCI



3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints are the safety and tolerability of MLN2480 (incidence of adverse events [AEs], serious adverse events [SAEs], dose-limiting AEs within the first cycle, and deaths; results of physical examinations, vital sign measurements, electrocardiogram [ECG] changes, Eastern Cooperative Oncology Group [ECOG] performance status, and hematology, blood chemistry, and urinalysis parameters).

3.2 Secondary Endpoints

The secondary endpoints are as follows:

- Preliminary antitumor activity of MLN2480 (overall response rate [ORR], progression-free survival [PFS], and duration of response [DOR])
- Pharmacokinetics of MLN2480 (maximum observed concentration [C_{max}], trough concentration [C_{trough}], first time to maximum concentration [t_{max}], $t_{1/2}$, renal clearance (CL_r), and area under the concentration-time curve [AUC])
- Pharmacodynamic activity of MLN2480 (such as inhibition of pERK and Ki67, and cPARP staining) based on tissue availability from tumor biopsy

3.3 Exploratory Endpoints

The exploratory endpoints are as follows:

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[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is a phase 1, multicenter, nonrandomized, open-label, dose escalation study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of MLN2480. This study will be the first to administer MLN2480 in humans. The study will be conducted in 2 phases (dose escalation and dose expansion) and will test 2 dosing schedules (Q2D and QW).

In the Dose Escalation phase, a 3 + 3 dose escalation design will be implemented to evaluate MLN2480 Q2D or QW in dose intervals with continuous dosing (no washout) prespecified in the Dose Escalation Algorithm. Patients in the Dose Escalation cohorts will be evaluated for dose-limiting toxicity (DLT) during the first cycle of treatment, and decisions regarding escalation to the next dose level, expansion of a dose level, or evaluation of an intermediate dose level will be determined based on DLT evaluation. Patients in the Dose Escalation phase may continue treatment for additional cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

The dose used for the Dose Expansion phase (MTD and/or RP2D) will be selected based on data from the Dose Escalation phase at the corresponding dosing schedule (Q2D or QW). The Dose Expansion phase may commence before establishing the MTD/RP2D upon medical determination of a safe dose that is lower than MTD/RP2D.

Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of MLN2480. Patients in the Dose Expansion phase will take MLN2480 orally Q2D or QW in 28-day cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

Patients who discontinue study treatment during Cycle 1 for reasons other than MLN2480-related toxicity will be replaced in the Dose Escalation phase of the study.

4.1.1 Q2D Dose Schedule

Q2D Dose Escalation Phase

In the Q2D Dose Escalation phase, a 3 + 3 dose escalation design will be used to evaluate MLN2480 orally Q2D, with continuous dosing (no washout). In the Q2D escalation cohorts, the first 3 patients with advanced solid tumors will receive a MLN2480 starting dose of 20 mg every other day for a 22-day cycle (11 doses). Upon implementation of Amendment 3, any ongoing dose escalation cohort will continue enrollment on the 22-day cycle schedule until the cohort is full and all patients have been evaluated for dose-limiting toxicity (DLT) (see Section 6.2). For all subsequent dose escalation and expansion cohorts, patients will be treated Q2D on a 28-day cycle (14 doses). Patients who began treatment on the 22-day cycle may switch from the 22-day to 28-day cycle upon safety confirmation of the 28-day cycle and agreement from the investigator and sponsor. The first dose escalation cohort on the 28-day cycle schedule will repeat the previously tolerated unit dose on the 22-day cycle. Administration of the same unit dose every other day in a 28-day cycle instead of a 22-day cycle represents a 27% increase in total cycle dose, which is less than the smallest (33%) increase in total cycle dose originally planned for the 22-day cycle in the Dose Escalation phase. After tolerability is confirmed when the same unit dose is administered every other day for 28 days, subsequent dose escalations in a 28-day cycle will consist of a 33% increase in both unit and total cycle dose.

Q2D Dose Expansion Phase

Once the MTD and/or RP2D of Q2D MLN2480 have been determined, or at the discretion of the sponsor, the study will continue to a Q2D Dose Expansion phase, which will enroll approximately 96 patients with locally advanced, metastatic, and/or unresectable melanoma and approximately 16 patients with any advanced solid tumor (excluding lymphoma). Patients with melanoma will be assigned to 1 of 6 Q2D melanoma cohorts based on tumor genotype and treatment history. Patients may be enrolled into 1 of 6 melanoma expansion cohorts based on previously documented genotype status, but may undergo a fresh biopsy at Screening for confirmation. A seventh cohort in the Q2D Dose Expansion phase, the PK Expansion cohort, will enroll a sufficient number of patients (approximately 16) with any advanced solid tumor (excluding lymphoma) to ensure that 12 patients complete protocol-specified dosing and PK assessments scheduled during Cycle 1.

4.1.2 QW Dose Schedule

QW Dose Escalation Phase

In the QW Dose Escalation phase, a 3 + 3 dose escalation design will be used to evaluate MLN2480 orally Q2D on Days 1, 8, 15, and 22 of a 28-day cycle. The first 3 patients with advanced solid tumors will receive a MLN2480 QW starting dose of 400 mg. Dose increases of 200 mg (ie, 600 mg, 800 mg, 1000 mg) will be made in each subsequent cohort until the MTD/RP2D is reached.

QW Dose Expansion Phase

Once the MTD and/or RP2D of QW MLN2480 have been determined, or at the discretion of the sponsor, the study will continue to a QW Dose Expansion phase. Approximately 32 patients, (up to 16 patients per cohort) with locally advanced, metastatic, and/or unresectable melanoma will be enrolled into 1 of 2 QW dose expansion cohorts based on tumor genotype and treatment history. Patients may be enrolled into the QW melanoma or solid tumor expansion cohorts based on previously documented genotype status, but may undergo a fresh biopsy at Screening for confirmation.

4.2 Number of Patients

A total of approximately 198 patients with solid tumors will be enrolled in this study. The first 15 to 30 patients will be recruited in approximately 2 US sites in the Q2D Dose Escalation phase; approximately 112 patients will be recruited in approximately 10 to 18 US and international sites for the Q2D Dose Expansion phase. Amendment 6 introduces new

dose cohorts that will follow a QW dosing schedule. Approximately 12 to 24 patients will be recruited in approximately 4 to 8 US sites in the QW Dose Escalation phase, and up to approximately 32 patients will be recruited in approximately 10 to 18 US and international sites for the QW Dose Expansion phase.

In the Q2D and QW Dose Escalation phases, the exact number of patients will depend on the number of dose escalation steps, and the number of patients per cohort, as per the 3 + 3 dose escalation design.

4.3 Duration of Study

The study period will consist of the Screening and Treatment periods. During the Screening period, patient eligibility for the study will be determined within 28 days prior to Day 1.

During the Treatment period, patients will take MLN2480 orally Q2D in 22- or 28-day treatment cycles or QW in 28-day treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months. Patients in the study for 4 years or longer will take MLN2480 Q2D in 12-week (84-day) treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason.

When patients discontinue study treatment, they should return to the study site 30 (+ 10) days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, to complete the End of Study visit procedures.

All MLN2480-related toxicities will be followed until the End of Study visit or until the toxicities have resolved, stabilized, or returned to baseline, whichever occurs later.

5. STUDY POPULATION

5.1 Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local patient privacy regulations.

2. Age ≥ 18 years at the time of informed consent or patient meets the minimum age of consent in accordance with national regulations (whichever is higher).

3. Dose Escalation phases (Q2D and QW): Patients with advanced solid tumors (excluding lymphoma, including melanoma) who have failed or are not candidates for standard therapies or for whom no approved therapy is available.

4. Dose Expansion phase (Q2D and QW): Patients with locally advanced, metastatic, and/or unresectable melanoma or solid tumors who meet the following cohort-specific criteria:

   Q2D Melanoma Expansion Cohorts

   - Cohort 1: BRAF mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.

   - Cohort 2: BRAF mutation-positive cutaneous melanoma, which in response to previous treatment with RAF inhibitors and/or MEK inhibitors, has 1) relapsed following an objective response, 2) failed to demonstrate an objective response, and/or 3) could not tolerate such a regimen due to unacceptable toxicity.

   - Cohort 3: NRAS mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.

   - Cohort 4: NRAS mutation-positive cutaneous melanoma, which in response to previous treatment with MEK inhibitors, has 1) relapsed following an objective response, 2) failed to demonstrate an objective response, and/or 3) could not tolerate such a regimen due to unacceptable toxicity.

- Cohort 5: BRAF/NRAS mutation-negative cutaneous melanoma (wild type), naïve to any prior anticancer therapy except ipilimumab, anti-PD-1, and anti-PDL-1 mAbs.

- Cohort 6: BRAF/NRAS mutation-negative melanoma (wild type), received at least 1 line of prior anticancer therapy. Cutaneous, uveal, or mucosal melanoma permitted in this cohort.

- (Cohort 7: Not a melanoma cohort. See below for information on the PK expansion cohort)

QW Melanoma Expansion Cohorts

- Cohort 8: Patients with BRAF mutation-positive cutaneous melanoma (approximately 16 patients total: approximately 8 patients who are naïve to prior therapy with RAF and MEK inhibitors and approximately 8 patients who have relapsed/are refractory to prior therapy with RAF or MEK inhibitors).

  Note: Enrollment into Cohort 8 is discontinued as of this amendment (Amendment 8).

- Cohort 9: NRAS mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.

5. Dose Expansion phase (Q2D): PK cohort:

   - **Cohort 7:** Patients with any advanced solid tumor (excluding lymphoma, but including melanoma) who have failed or are not candidates for standard therapies or for whom no approved therapy is available.

6. Dose Expansion phases (Q2D and QW), excluding Cohort 7 (PK Cohort): At least 1 measurable lesion, according to RECIST, version 1.1 (see Section 14.3), which has not been treated previously with radiotherapy. A newly arising lesion in a previously irradiated field is acceptable.

7. Q2D Dose Expansion phase, Cohorts 1-6 only: At least 8 patients per cohort must be able to have paired tumor biopsies conducted for analysis of pharmacodynamic biomarkers (see Table 1-13)

8. QW Dose Expansion phase (Cohorts 8 and 9): A minimum of 8 patients must be able to have paired tumor biopsies conducted for analysis of pharmacodynamic biomarkers (see Table 1-13)

9. For patients undergoing biopsy procedures: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) must be within the normal range and platelet count > 75,000/mm^3 within 48 hours of biopsy.

10. ECOG performance status ≤ 1.

11. Dose Escalation and PK Expansion cohorts: Adequate tissue sample from either archival CCI tissue or fresh biopsy of tumor at Screening for tumor genotyping (Table 1-13).

12. Previous chemotherapy and hormone therapy must be completed at least 4 weeks or 4 half lives, whichever occurs first, prior to administration of MLN2480. Previous immunotherapy/ monoclonal antibody use must be completed at least 4 weeks prior to administration of MLN2480. In addition, radiation therapy must be completed at least 3 weeks prior to administration of MLN2480. All associated toxicity from previous therapies must be resolved to ≤ Grade 1 prior to administration of MLN2480. Prior treatment with anti-PD-1 and anti-PDL-1 mAbs is permitted with a washout period of ≥ 6 weeks, provided there is no observed tumor shrinkage during that time relative to the previous progression scan.

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

14. Thyroid function tests consistent with stable thyroid function. (Patients on a stable dose of thyroid replacement therapy for a suggested minimum of 12 weeks prior to Cycle 1, Day 1 are eligible.)

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

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

17. 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, 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, 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.)

For further details of contraceptive requirements for this study, please refer to Section 6.6.2.2.

18. Suitable venous access for the study-required blood sampling, including PK assessments of MLN2480.

5.2 Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the time point specified in the individual criterion listed:

1. History of any major disease that might interfere with safe protocol participation, as determined by the investigator.
2. Dose Expansion phase, Cohorts 1, 3, and 5 only: Previous treatment with RAF or MEK inhibitors.

3. Laboratory values:

    - Absolute neutrophil count (ANC) ≤ 1500/μL
    - Platelet count ≤ 75,000/μL
    - Hemoglobin < 9 g/dL (hemoglobin may be supported by transfusion, erythropoietin, or other approved hematopoietic growth factors)
    - Serum bilirubin ≥ 1.5 × upper limit of normal (ULN) or ≥ 2 × ULN if patient is known to have Gilbert's Disease as the only underlying hepatic disorder
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥ 2.5 × ULN (AST and ALT ≥ 5 × ULN for patients with liver metastasis)
    - Serum creatinine ≥ 2.0 mg/dL
    - Brain metastasis, unless previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery and the disease has been stable for at least 2 months without steroid use or on a stable dose of steroids for at least 1 month prior to the first dose of MLN2480

4. Dose Expansion phase: No other active malignancy
5. Current enrollment in any other investigational treatment study.
6. Evidence of current uncontrolled cardiovascular conditions, including but not limited to clinically significant cardiac arrhythmias, congestive heart failure, angina, or myocardial infarction, within the past 6 months.
7. Prior investigational agents for malignant or non-malignant disease within 4 weeks prior to Day 1.
8. Active hepatitis or human immunodeficiency virus infection.
9. Active bacterial or viral infection.
10. Female patients who are pregnant or currently breastfeeding.
11. Major surgery within 28 days of Day 1.

12. Inability to comply with study requirements.

13. Refractory nausea and vomiting, malabsorption, or significant bowel or stomach resection that would preclude adequate absorption of MLN2480.

14. Treatment with any of the following strong or moderate CYP3A/CYP2C inducers within 14 days before the first dose of study drug: rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, phenobarbital, primidone, St. John's Wort, bosentan, nafcillin, and modafinil.

15. Treatment with gemfibrozil (strong CYP2C8 inhibitor) within 14 days before the first dose of study drug.

16. Other unspecified reasons that, in the opinion of the investigator or Millennium, make the patient unsuitable for enrollment.

6. STUDY DRUG

6.1 Study Drug Administration

Millennium will provide MLN2480 to study sites. Refer to Sections 6.9 through 6.10 for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

Patients in the Dose Escalation phase will receive MLN2480 Q2D for a 22- or 28-day cycle (11 or 14 doses) or QW for a 28-day cycle (4 doses). Patients in the Dose Expansion phase will receive MLN2480 Q2D for a 28-day cycle (14 doses) or QW for a 28-day cycle (4 doses), followed by additional cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. Patients in the Q2D PK Expansion cohort will have a modified dosing schedule only for Cycle 1: MLN2480 Q2D on Days 1 through 21 of the 28-day cycle (11 doses), with no drug administered on Days 22 through 28. For Cycle 2 and beyond, the PK Expansion cohort will follow the standard dosing schedule of MLN2480 (Q2D for a 28-day cycle [14 doses], followed by additional 28-day cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason). The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months. If MLN2480 is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of MLN2480. Patients should take their MLN2480 tablets at the same time with approximately 6 ounces (180 mL) of water on dosing days. Patients should be encouraged to take their doses at approximately the same time on each dosing day.

Other oral medications should not be taken within 1 hour before or after taking MLN2480. If emesis occurs after taking MLN2480, symptoms should be managed with standard antiemetic therapy, and a repeat (replacement) dose of MLN2480 should not be taken. Refer to the Pharmacy Manual for details on administration.

Missed doses should be taken within 12 hours. If the patient does not remember to take the dose within 12 hours, this dose should be skipped and the next dose should be taken as scheduled. Doses should not be doubled to make up for missed doses. All missed doses or doses administered within approximately 1 hour before a vomiting episode should be recorded in the electronic case report form (eCRF).

The Treatment period will consist of continuous 22- or 28-day cycles. Eligible patients will report to the study site to receive 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 dose of MLN2480 at home. Patients will continue to take MLN2480 orally Q2D in 22- or 28-day treatment cycles or QW in 28-day treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason.

6.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Dose-limiting toxicity is defined as an AE that the investigator considers to be at least possibly related to study treatment. Toxicities will be graded according to NCI CTCAE, version 4.03. Dose-limiting toxicities will be assessed for each patient during the DLT observation period and will be defined as any of the following:

- Grade 4 neutropenia lasting ≥ 7 consecutive days
- Febrile neutropenia (defined as ANC ≤ 1000 cells/μL and fever ≥ 38.5°C) or documented infection ≥ Grade 3 with ANC ≤ 1000 cells/μL

- Grade 4 thrombocytopenia (< 25,000/μL), MLN2480-related thrombocytopenia requiring platelet transfusion, or MLN2480-related bleeding requiring medical attention

- Treatment delays of ≥ 14 days due to any toxicity

- ALT or AST toxicities:

  - ALT or AST > 7.5 × ULN for greater than 14 days

  - AST or ALT > 7.5 × ULN that is accompanied by an elevation in total bilirubin of > 3 × ULN (not explained by obstruction) regardless of duration

- Nonhematological toxicity ≥ Grade 3 with the following exceptions:

  - 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 MLN2480 may receive antiemetic or antidiarrheal medication prior to subsequent doses of MLN2480

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

  - Fatigue ≥ Grade 3 for ≤ 7 days will not be considered a DLT

  - Development of keratoacanthomas or skin carcinoma will not be considered a DLT unless unusually aggressive or metastatic.

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 platelet counts return to > 50,000/μL.

Patients will be evaluable for DLT if they either experience DLT in Cycle 1 or they receive at least 75% of the planned doses of study drug and have sufficient follow-up data to determine whether DLT occurred. Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose

levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities and if there is evidence for cumulative MLN2480-related toxicity, this may influence decisions regarding dose escalation and the dose recommended for use in subsequent clinical trials.

If no DLT is observed during the first cycle of treatment in the initial 3 patients enrolled to a given dose level, then 3 new patients will be enrolled at the next higher dose level. Alternatively, if 1 of the initial 3 patients treated at a given dose level experiences a DLT, then 3 additional patients will be added to that same dose level. Dose escalation can proceed only if none of these additional 3 patients experiences DLT. Dose escalation is stopped if DLT occurs in ≥ 2 patients at any given dose level, regardless of the total number of patients treated at that dose level. The highest dose level that generates DLT in 0/3 or 1/6 patients is then considered to be the MTD. Once the MTD has been identified, additional patients will be treated at the MTD and/or the RP2D in the Dose Expansion phase to establish greater confidence in its safety and suitability for use in subsequent clinical trials (see the Dose Escalation Algorithm).

Patients will not be included in either the numerator or denominator when calculating the nominal rate of DLT at any given dose level if 1 of the following occurs:

- A patient receives less than 75% of the planned doses during the first cycle of therapy or does not have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred.
- A patient discontinues the study for reasons other than DLT before they have completed Cycle 1 of treatment.

Such patients will be replaced. Patients who experience a DLT during the Dose Expansion phase may be allowed to continue treatment with MLN2480 at a dose level below that which was associated with the DLT (see Section 6.5).

6.3 Dose Escalation Phase

The Dose Escalation phases will include approximately 54 patients (30 in the Q2D escalation cohorts and 24 in the QW escalation cohorts) with solid tumors, including locally advanced, metastatic, and/or unresectable melanoma; who have failed or are not candidates for standard therapies or for whom no approved therapy is available. A 3 + 3 dose escalation design will be used, with the first 3 Q2D patients receiving the starting dose of 20-mg

MLN2480 orally Q2D for a 22-day cycle (11 doses; first dose on Day 1 and last dose on Day 21) and first 3 QW patients receiving the starting dose of 400 mg MLN2480 orally QW for a 28-day cycle (4 doses; first dose on Day 1 and last dose on Day 22), followed by additional cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason, or until 12 months of treatment have been administered. Upon implementation of Amendment 3, any ongoing dose escalation cohort will continue enrollment on the 22-day cycle schedule until the cohort is full and all patients have been evaluated for dose-limiting toxicity (DLT) (see Section 6.2). For all subsequent dose escalation cohorts, patients will be treated Q2D on a 28-day cycle (14 doses). Patients who began treatment on the 22-day cycle may switch from the 22-day to 28-day cycle upon safety confirmation of the 28-day cycle and agreement from the investigator and sponsor. The previously tolerated unit dose administered Q2D in the 22-day cycle will be administered as the first unit dose for the 28-day cycle. Administration of the same unit dose every other day in a 28-day cycle instead of a 22-day cycle represents a 27% increase in total cycle dose, which is less than the smallest (33%) increase in total cycle dose originally planned for the 22-day cycle in the Dose Escalation phase. After tolerability is confirmed when the same unit dose is administered every other day in a 28-day cycle instead of a 22-day cycle, subsequent dose escalations in a 28-day cycle will consist of a 33% increase in both unit and total cycle dose. Regardless of cycle length, dosing is every other day on a continuous basis, with no treatment-free period between cycles (except for Cycle 1 in the PK Expansion cohort).

Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of MLN2480.

Dose Escalation Guidelines

The DLT observation period for a dose cohort is defined as Cycle 1, Day 1 to either Cycle 1, Day 22 (22-day cycle), or Cycle 1, Day 28 (28-day cycle). Safety data and available PK data from the DLT observation period of a given dose cohort will be reviewed prior to escalating the dose to the next cohort (see Dose Escalation Algorithm).

To provide patients the opportunity to derive maximum clinical benefit from study drug, patients in the dose escalation phase in dose cohorts 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 study drug, no dose interruptions related to study drug toxicities, and no delays of greater than 1 week in starting a cycle due to study drug

toxicities. In order for a patient to escalate to the next dose level, the level above the proposed escalated dose must be deemed safe.

The Sponsor, in collaboration with the Principal Investigators, will determine if intrapatient dose escalation is appropriate on a case-by-case basis. Patients who have had any dose reductions will not be permitted to dose escalate.

For Q2D dose escalation, the first patient in each dose cohort must be observed for safety for at least 6 days before the next 2 patients can be enrolled. No waiting period will be required between the 2 subsequent patients. For the initial dose increase in the QW Dose Escalation phase (from 400 mg to 600 mg), patients will be enrolled in the 600 mg dose cohort in a staggered manner, with 1 week in between each patient. No waiting period will be required in subsequent QW dose cohorts.

Enrollment of patients in successive cohorts will not begin until at least 21 days for 22-day cycles or 27 days for 28-day cycles after the last patient in the previous cohort has received their first dose of MLN2480 and the End-of-Cohort meeting has occurred.

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, Days 1 to 22 or 28). During this meeting, the sponsor and investigators will review and discuss AEs, laboratory results, available pharmacokinetics data, and other relevant data to determine if the dose escalation criteria have been met and if dose escalation may proceed. Subsequent cohorts will only be opened for enrollment after all investigators have agreed to the dose escalation.

The Q2D dose escalation will follow a modified Fibonacci schema (sequential dose escalation increments of approximately 100%, 100%, 67%, 50%, 40%, and 33% thereafter) (see Table 6-1). During the transition from a 22-day to a 28-day cycle, the unit dose will not be increased but the total cycle dose will be increased by 27%.

Table 6-1 Q2D Planned Dose Levels

Dose Level	Dose Increase Factor	Dose (mg/day)
1	Starting dose	20
2	100%	40
3	100%	80
4	67%	135
5	50%	200
6	40%	280[a]

Abbreviations: DLT=dose-limiting toxicity.
The first cohort dosed at the 28-day cycle will repeat the last safe unit dose at the 22-day cycle.
a Additional dose levels will continue to be explored at a dose increase factor of 33% until > 1 out of 6 patients has a DLT.

Consequently, in the absence of more than 1 DLT occurring in a given cohort or the MTD being established, it is anticipated that the doses for the sequential cohorts will be 20, 40, 80, 135, 200, and 280 mg MLN2480 Q2D, with 33% dose escalation increments thereafter until the MTD is established.

The QW dose escalation will follow sequential dose escalation increments of 200 mg increments QW until MTD is reached) (see Table 6-2).

Table 6-2 QW Planned Dose Levels

Dose Level	Dose Increase Factor	Dose (mg/wk)
1	Starting dose	400
2	50%	600
3	33%	800
4	25%	1000

Abbreviations: DLT=dose-limiting toxicity.
a Additional dose levels increasing by 200 mg will continue to be explored until > 1 out of 6 patients has a DLT.

Consequently, in the absence of more than 1 DLT occurring in a given cohort or the MTD being established, it is anticipated that the doses for the sequential cohorts will be 400, 600, 800, and 1000 mg MLN2480 QW, with 200 mg QW dose escalation increments thereafter until the MTD is established.

Dose escalation parameters are as follows:

- If 0 of 3 patients in a dose cohort experience a DLT in the DLT observation period, enrollment of patients into the next dose cohort will begin following the End-of-Cohort meeting.

- If 1 of 3 patients in a dose cohort experiences a DLT in the DLT observation period, an additional 3 patients will be treated in this dose cohort. If < 2 patients in a given dose cohort experience a DLT, enrollment into the next dose cohort can begin following the End-of-Cohort meeting.

- If ≥ 2 patients in a dose cohort experience a DLT in the DLT observation period, that dose will be considered to have exceeded the MTD.

- Depending on the nature of the DLTs in the preceding dose cohort, an additional intermediate dose cohort may be evaluated before proceeding to the Dose Expansion phase of the study.

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 MLN2480.

6.4 Dose Expansion Phase

The Dose Expansion phase will include patients with locally advanced, metastatic, and/or unresectable melanoma (melanoma expansion cohorts), Approximately 128 patients with melanoma will be enrolled into 1 of 8 dose expansion cohorts (approximately 16 patients per cohort), based on tumor genotype and treatment history.

Q2D Dose Expansion Cohorts

- Cohort 1: BRAF mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.

- Cohort 2: BRAF mutation-positive cutaneous melanoma, which in response to previous treatment with RAF inhibitors and/or MEK inhibitors, has 1) relapsed following an objective response, 2) failed to demonstrate an objective response, and/or 3) could not tolerate such a regimen due to unacceptable toxicity.

- Cohort 3: NRAS mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.

- Cohort 4: NRAS mutation-positive cutaneous melanoma, which in response to previous treatment with MEK inhibitors, has 1) relapsed following an objective response, 2) failed to demonstrate an objective response, and/or 3) could not tolerate such a regimen due to unacceptable toxicity.

- Cohort 5: BRAF/NRAS mutation-negative cutaneous melanoma (wild type), naïve to any prior anticancer therapy except ipilimumab, anti-PD-1, and anti-PDL-1 mAbs.

- Cohort 6: BRAF/NRAS mutation-negative melanoma (wild type), received at least 1 line of prior anticancer therapy. Cutaneous, uveal, or mucosal melanoma permitted in this cohort.

- (Cohort 7: Not a melanoma cohort. See below for information on the PK expansion cohort)

QW Melanoma Expansion Cohorts

- Cohort 8: BRAF mutation-positive cutaneous melanoma (approximately 16 patients total: approximately 8 patients who are naïve to prior therapy with RAF and MEK inhibitors, and approximately 8 patients who relapsed/refractory to prior therapy with RAF or MEK inhibitors).

  Note: Enrollment into Cohort 8 is discontinued as of this amendment (Amendment 8).

- Cohort 9: NRAS mutation-positive cutaneous melanoma, naïve to prior therapy with RAF and MEK inhibitors.

Individual Dose Expansion cohorts may be opened or closed sequentially or in parallel at the sponsor's discretion, based on emerging data. Patients in the Q2D melanoma expansion cohorts will take the selected dose of MLN2480 orally every other day in 28-day cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. Patients in the QW dose expansion cohorts will take the selected dose of MLN2480 orally once weekly (on Days 1, 8, 15, and 22) in 28-day cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason.

Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of MLN2480. A fresh tumor biopsy for genotyping will be required for all patients in the 6 Q2D dose expansion cohorts and will be requested for the QW dose expansion cohorts at Screening; archived tumor tissue will also be requested if available. A postdose fresh biopsy on Day 21 of Cycle 1 will also be collected from at least 8 patients in each Q2D melanoma expansion cohort. The postdose fresh biopsy may need to be collected in more than the specified patients in each cohort/ treatment schedule to ensure evaluable biopsies are collected. After the specified pairs of Screening and postdose biopsies have been confirmed to be evaluable from a cohort, the postdose biopsy for the remaining patients in that cohort will be optional. The postdose fresh biopsy should be collected in a patient only if an evaluable fresh (or archived) biopsy was collected at Screening. For patients on the QW dose schedule, a predose fresh biopsy will also be requested on Day 22 of Cycle 1 from up to 8 evaluable patients (if archived tissue not available or not evaluable). Evaluable biopsy pairs collected at Screening and Day 21 (Q2D) or Day 22 (QW) of Cycle 1 will be used for pharmacodynamic biomarker analysis.

A seventh cohort in the Q2D Dose Expansion phase, the PK Expansion cohort, will include patients with any advanced solid tumor (except lymphoma but including melanoma) who have failed or are not candidates for standard therapies or for whom no approved therapy is available. In addition to contributing to the evaluation of safety, tolerability, and preliminary antitumor activity, the PK Expansion cohort will be used to more fully characterize MLN2480 PK. Patients in the PK Expansion cohort will take the selected dose of MLN2480 orally Q2D on Days 1 through 21 of the 28-day cycle for Cycle 1; dosing for Cycle 2 and beyond will follow the standard Q2D dosing in 28-day cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. An archival or fresh tumor tissue sample will be obtained at Screening for genotyping of patients as specified in Table 1-13. No paired biopsies for PD analysis will be collected in the PK Expansion cohort.

The maximum duration of treatment for all patients in the Dose Expansion phase will be 1 year unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

6.5 Dose Modification Guidelines

6.5.1 Dose Escalation Phase

Any patient in the Dose Escalation phase whose toxicity meets a criterion of a DLT will discontinue study treatment. If necessary, MLN2480 dose reductions or dose interruptions will be allowed in the following circumstances:

- If the patient experiences Grade 3 or 4 fatigue, the patient will stop taking MLN2480. The patient may resume taking the original dose of MLN2480 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 MLN2480. The patient may resume taking the original dose of MLN2480 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 MLN2480. If the AE resolves to ≤ Grade 2 in ≤ 14 days, the patient can resume taking MLN2480. If the AE does not resolve to ≤ Grade 2 after 14 days, the patient must discontinue study treatment.

6.5.2 Dose Expansion Phase

Depending on the nature and severity of an AE, and under discretion of the investigator with agreement from the sponsor, the following dose modifications are recommended:

- Patients who experience a Grade 2 related AE may have their MLN2480 dose decreased to 160 mg Q2D or by 1 dose level (minus 200 mg QW).

- Patients who experience a Grade 3 related AE may have their MLN2480 dose decreased to 140 mg Q2D or by 1 dose level (minus 200 mg QW).

- 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.

In addition, consideration will be given on a case-by-case basis for patients on the Q2D dose schedule to transfer to the QW dose schedule for the management of toxicity. A patient may only be switched from the Q2D schedule to the QW schedule pending agreement between the investigator and Sponsor.

The sponsor must be notified of any MLN2480 dose modifications.

6.6 Concomitant Medications and Procedures

Premedications and concomitant mediations and therapy will be recorded in the eCRF from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever occurs first.

See Section 6.6.1 for a list of prohibited medications and therapies and Section 6.6.2.3 for medications or procedures that are restricted or should be used cautiously.

6.6.1 Excluded Concomitant Medications and Procedures

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

In vitro data indicates that MLN2480 is metabolized by aldehyde oxidase and CYPs 2C8, 2C9, 2C19, and 3A4, with relative contributions of 49%, 33%, 8%, 7%, and 4%, respectively. Based on this data, concomitant use of strong and moderate inducers of CYP3A and CYP2C enzymes and strong inhibitors of CYP2C8 is prohibited during the study.

- Strong and Moderate Inducers of CYP3A and CYP2C enzymes: rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, phenobarbital, primidone, St. John's Wort, bosentan, nafcillin, and modafinil

- Strong CYP2C8 inhibitor: gemfibrozil

6.6.2 Precautions and Restrictions

6.6.2.1 Hematology and Blood Chemistry

Hematology results and blood chemistry results will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle according to the Schedule of Events. 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 > 1,000/μL and platelet counts return to > 50,000/μL.

6.6.2.2 Pregnancy

It is not known what effects MLN2480 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the Screening visit, or
- Surgically sterile, or
- Agree to practice true abstinence from sexual intercourse, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing of the informed consent form (ICF) through 120 days (4 months) after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.), or

- Agree to practice 2 reliable methods of contraception, at the same time, from the time of signing of the ICF through 120 days (4 months) after the last dose of study drug. The 2 methods of reliable 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

Female patients must also agree not to donate ova (egg cells) during participation in the study or for 120 days (4 months) following the last dose of study drug.

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

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

- Practice effective barrier contraception during the entire study Treatment period and through 120 days (4 months) after the last dose of study drug.

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.

6.6.2.3 Medications and Procedures

In vitro data indicates that MLN2480 may inhibit CYP2C8. Therefore, coadministration of MLN2480 with substrates predominantly or substantially metabolized by CYP2C8 should be used with caution, including but not limited to cerivastatin, rosuvastatin, repaglinide, rosiglitazone, pioglitazone, amiodarone, chloroquine, amodiaquine, and montelukast.

MLN2480 is an in vitro inhibitor of the efflux transporter BCRP. On the basis of clinical exposure observed to date, there is a potential risk for MLN2480 to inhibit transport of co-administered drugs that are substrates of BCRP. Although currently there are limited examples of clinically meaningful drug-drug interactions related to BCRP inhibition, information on BCRP-mediated drug interactions continues to evolve. Consequently, caution should be exercised when MLN2480 is administered concurrently with substrates of BCRP. These include, but are not limited to, HMG-CoA reductase inhibitors (rosuvastatin, pitavastatin, cerivastatin), antibiotics (ciprofloxacin, norfloxacin, ofloxacin erythromycin, nitrofurantoin), calcium channel blockers (dipyridamole, nitrendipene, azidopine), sulfasalazine, cimetidine, methotrexate, and glyburide.

MLN2480 did not inhibit P-gp in vitro at concentrations up to 30 μM. A clinically meaningful interaction with co-administered P-gp substrates is not anticipated at systemic sites of transport (liver, kidney, blood-brain barrier). However, as the possibility of inhibition of intestinal P-gp transport by clinical doses of MLN2480 cannot be ruled out due to potentially higher concentrations in the intestinal lumen (> 30 μM), cautious use and close monitoring of patients is advised as a precautionary measure when an orally administered P-gp substrate with a narrow therapeutic index (eg, digoxin and cyclosporine) is taken concomitantly with MLN2480.

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

Blood transfusions are permitted after Cycle 1 but must be administered either before dosing or at least 1 hour after dosing. Growth factors may be administered after Cycle 1 is completed.

Prophylactic medications should not be administered until an AE occurs during Cycle 1. Prophylactic medications are allowed in subsequent cycles.

Patients undergoing tumor biopsy procedures who are receiving ongoing therapy with an anticoagulant (eg, aspirin, clopidogrel [Plavix®], warfarin, or heparin [including low molecular-weight heparin]) must be able to safely stop therapy with these medications 7 days before the first biopsy and not resume therapy with these medications until 7 days after the last biopsy.

6.6.2.4 Food

Patients should not eat or drink (with the exception of water) for 2 hours before and 2 hours after administration of MLN2480 doses.

6.6.2.5 Photosensitivity

Photosensitivity is a recognized class effect of RAF kinase inhibitors. Patients should therefore use caution and minimize exposure to sunlight and UV light.

6.7 Recommendations for Management of Clinical Events: Dose Expansion Phase

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, and the eye exam should include slit lamp examination of the cornea, retinal photographs, and intraocular pressure measurement as clinically indicated. 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.

Increased Creatine Kinase Levels

Increased creatine kinase (CK) levels have been observed with MLN2480 administration. While an increase in CK level alone (asymptomatic) is not reason to reduce the dose of

MLN2480, it is important to rule out an accompanying clinical condition. See the following recommendations in Table 6-3.

Table 6-3 Management of Elevated Creatine Kinase Levels

AE Grade	Event Definition	Recommendation
Grade 1	> ULN – 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 – 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 dipstick, heme +, RBC -) • NOTE: Consider reducing dose of MLN2480 from 200 mg Q2D to 160 mg Q2D
Grade 3/ Grade 4	> 5 × ULN – 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 dipstick, heme +, RBC) • In the presence of chest pain, test levels of Troponin I or Troponin T • NOTE: Consider holding administration of MLN2480 until value has decreased to Grade 1 or baseline

Source: Common Terminology Criteria for Adverse Events (CTCAE), v4.03.[37]

Rash

Rashes (maculo-papular, dermatitis acneiform, and pruritus) have been observed with MLN2480 administration. 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.

Should a rash occur, the following recommendations should be followed:

Table 6-4 Management of Rash

AE Severity	Event Definition	Recommendation
Grade 1	Macular or papular eruption or erythema without associated symptoms	• Cold compresses • Oral anti-histamines • 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 < 50% 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 dose reduction to 160 mg Q2D after discussion between the investigator and sponsor.
Grade 3 or Higher	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥ 50% BSA Generalized exfoliative, ulcerative, or bullous dermatitis	• MLN2480 should be delayed until the rash improves • 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 • Consider dose reduction to 140 mg or holding administration of MLN2480 until resolved to Grade 1 or baseline

Source: Guidelines for Rash/Dermatitis adapted from Lemech and Arkenau, 2012.[38]

NOTE: Should a Grade 2 or 3 rash occur, photographic documentation is recommended.

Management of Cardiac Events

Cardiac events, including heart failure and atrial fibrillation, have been observed with MLN2480 administration. Should a cardiac event occur, the following recommendations should be followed:

Event Definition	Recommendation
Asymptomatic, absolute decrease in LVEF of 10%-20% from pretreatment value	Do not modify the dose of MLN2480.
• Symptomatic congestive heart failure, or • 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 Description of Investigational Agents

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 receive only the initial drug product.

The MLN2480 drug product is formulated as an immediate-release tablet for oral administration. The description of 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 tables 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.

MLN2480 is manufactured in accordance with Good Manufacturing Practices.

6.9 Preparation, Reconstitution, and Dispensation

The pharmacist or medically qualified staff will dispense MLN2480 tablets to enrolled patients. The individual preparing MLN2480 should first review dispensing instructions provided in the Pharmacy Manual.

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.

6.10 Storage, Handling, and Accountability

MLN2480 tablets (20 mg, 70 mg, and 100 mg) are to be stored at 20°C to 25°C (68°F-77°F) and protected from excessive humidity, in a monitored, locked storage cabinet with limited access. Refer to the Pharmacy Manual for allowable storage and shipping temperature excursions.

Study treatment must be stored in a secure location. Accountability for study treatment is the responsibility of the investigator. Study site staff must instruct patients on how to store MLN2480 tablets.

The investigator must destroy or return all unused MLN2480 study drug as instructed by Millennium. Refer to the Pharmacy Manual for complete drug destruction policies.

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (patient-by-patient accounting), amount returned by the patient, and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all unused MLN2480 study drug supply must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of MLN2480 supplied, dispensed, and subsequently destroyed or returned to Millennium. A written explanation must be provided for any discrepancies.

Refer to the Pharmacy Manual for complete instructions regarding storage, handling, and accountability.

7. STUDY CONDUCT

This study 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, Organizations, and Systems

The contact information for the Millennium project clinician for this study, clinical laboratories, and the Contract Research Organization (CRO) 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 for the Dose Expansion phase, 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 electronic CRFs by a remote data capture (RDC) system (Inform).

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 patient to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

This is a phase 1 study that incorporates a Dose Escalation phase and a Dose Expansion phase at the MTD and/ or RP2D. In the Dose Escalation phase, a 3 + 3 dose escalation design will be used, with the first 3 Q2D patients receiving the MLN2480 starting dose of 20 mg orally Q2D for a 22-day cycle (11 doses) and the first 3 QW patients receiving the MLN2480 starting dose of 400 mg orally QW for a 28-day cycle (4 doses). Upon implementation of Amendment 3, any ongoing dose escalation cohort will continue enrollment on the 22-day cycle schedule until the cohort is full and all patients have been evaluated for dose-limiting toxicity (DLT) (see Section 6.2). For all subsequent dose escalation and dose expansion cohorts, patients will be treated Q2D or QW on a 28-day cycle (14 doses or 4 doses, respectively). Patients who began treatment on the 22-day cycle may switch from the 22-day to 28-day cycle upon safety confirmation of the 28-day cycle and agreement from the investigator and sponsor. The previously tolerated unit dose administered Q2D in a 22-day cycle will be readministered Q2D in a 28-day cycle. Escalation from the last safe dose at a 22-day cycle to a 28-day cycle represents a 27% increase in total cycle dose, which is less than the smallest (33%) increase in total cycle dose originally planned for the Dose Escalation phase.

Once the MTD and/or RP2D of MLN2480 have been determined for a 28-day cycle, or upon discretion of the sponsor, the study will continue to a Dose Expansion phase. The dose used for the Dose Expansion phase will be selected based on data from the Dose Escalation phase (MTD and/ or RP2D). The Dose Expansion phase will test MLN2480 in patients with locally advanced, metastatic, and/or unresectable melanoma (for Q2D dosing, Cohorts 1-6, for QW dosing Cohort 9), or in patients with advanced solid tumors, excluding lymphoma but including melanoma (Cohort 7). Tumor genotype is likely to serve as a predictor of response for patients with melanoma, and patients in dose expansion will be assigned to 1 of 8 overall cohorts on the basis of tumor genotype and treatment history. Patients may be enrolled into 1 of the 8 expansion cohorts on the basis of previously documented genotype status, but may undergo a fresh biopsy at Screening for confirmation.

Cohort 7 in the Q2D Dose Expansion phase, the PK Expansion cohort, will include patients with any advanced solid tumor (excluding lymphoma but including melanoma) who have failed or are not candidates for standard therapies or for whom no approved therapy is available.

7.4 Study Procedures

Each patient must sign and date an informed consent form (ICF) before undergoing any study-specific procedures unless those procedures are performed as part of the patient's standard of care.

Enrollment in the study is defined as the time of initiation of the first dose of study drug. Additional procedures for completion of the enrollment information are described in the Study Manual.

A detailed visit-by-visit schedule of study procedures is provided in the Q2D Schedules of Events and the QW Schedules of Events.

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 MLN2480. Procedures conducted during the Screening period that are performed within 3 days of Cycle 1, Day 1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified. 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 Q2D Schedules of Events for timing of all assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 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.

7.4.2 Patient Demographics

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

7.4.3 Medical History

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

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Q2D Schedules of Events or the QW Schedules of Events. Any clinically relevant findings are to be documented.

7.4.5 Eastern Cooperative Oncology Group Performance Status

Performance status is to be assessed using the ECOG scale (see Section 14.1 for a description of the scale) at the times specified in the Q2D Schedules of Events or the QW Schedules of Events.

7.4.6 Height and Weight

Height will be measured only during Screening. Body weight will be measured at the times specified in the Q2D Schedules of Events or the QW Schedules of Events.

7.4.7 Vital Signs

Vital sign measurements, including body temperature, measurement of diastolic and systolic blood pressure, and heart rate will be assessed as specified in the Q2D Schedules of Events or the QW Schedules of Events. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

7.4.8 Pregnancy Test

A pregnancy test will be obtained for women of childbearing potential as specified in the Q2D Schedules of Events or the QW Schedules of Events. A serum pregnancy test is required at the Screening and EOS visits; the Cycle 1, Day 1 pregnancy test can be serum or urine.

The Screening results must be available and negative prior to enrollment.

7.4.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the eCRF from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever occurs first. See Sections 6.6.1 and 6.6.2.3 for a list of medications and therapies that are prohibited or to be used cautiously during the study.

For patients in the expansion cohorts only, details of prior medications will be collected as part of their medical history; however, details of prior medications may also be retrospectively collected for patients of interest in the Dose Escalation phase.

7.4.10 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Q2D Schedules of Events or the QW Schedules of Events. Refer to Section 9 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.11 Enrollment

Enrollment is defined as the time of initiation of the first dose of study drug.

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

7.4.12 Multiple Gated Acquisition Scan and/or Echocardiogram

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

7.4.13 Electrocardiograms

ECGs will be reviewed at the site, including single safety ECGs and triplicate ECGs. All ECGs will also be sent to a central vendor for storage for potential future analysis. Additional information regarding the collection and transferring of ECGs can be found in the ECG manual.

Any findings from ECGs collected after study drug administration on Cycle 1, Day 1 will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

Predose ECGs should be completed within 1 hour before the start of dosing. When the timing of a PK, biomarker, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

The dates and exact times of ECG recordings should be recorded. Although the number of ECG measurements will not be increased, the timing of ECG measurements may be changed if emerging data indicate that an alteration in ECG sampling scheme is needed.

Electrocardiogram parameters will include PR, RR, QT, QTc, QRS, and ventricular rate.

7.4.13.1 Single ECGs

A single 12-lead ECG will be collected at Screening in all patients to assess eligibility. Additional single ECGs will be collected in Cycle 2 in all cohorts of the Expansion Phase and in Cycle 3 and all subsequent cycles in all patients (including at the End of Study visit). Refer to the Q2D Schedules of Events for timing of single ECGs.

7.4.13.2 Triplicate ECGs

All triplicate ECGs will be stored at a central reading laboratory for potential future reading if deemed necessary by the sponsor.

Triplicate 12-lead ECG recordings will be required in the Dose Escalation and PK Expansion cohorts at the time points specified in the Q2D Schedules of Events, Table 1-3, Table 1-6, and Table 1-12. They will not be performed in the dose expansion cohorts.

The triplicate ECG recordings will be performed in triplicate (approximately 2 to 5 minutes apart) after a 5-minute period of rest in the supine position and should be completed immediately before the corresponding PK blood draw.

7.4.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally.

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Q2D Schedules of Events or the QW Schedules of Events.

Hematology

- 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
- Neutrophils (ANC)

Blood Chemistry

- Blood urea nitrogen
- Creatinine
- Bilirubin (total)
- ALT
- Glucose
- Albumin
- Alkaline phosphatase
- AST
- Lactate dehydrogenase
- Thyroid function test
- Calcium
- Chloride
- Carbon dioxide
- Creatine kinase
- Potassium
- Sodium

Urinalysis

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

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 platelet counts return to > 50,000/µL.

7.4.15 Disease Assessment

At Screening, all sites of disease should be imaged by computed tomography (CT). If the anatomic region cannot be adequately imaged by CT, magnetic resonance imaging (MRI) may be used instead. The same imaging modality utilized at Screening for a particular site of disease must remain consistent throughout all subsequent disease assessments, which will be performed every 2 cycles after starting MLN2480 treatment, as described in the Q2D Schedules of Events or the QW Schedules of Events. Objective assessments will be performed at each time point, using modified RECIST criteria (version 1.1). RECIST criteria are described in Section 14.3. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents.

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

7.4.16 Dermatological Examination

All patients will be assessed by the investigator or a consulting dermatologist for skin lesions, especially for keratoacanthomas and squamous cell carcinomas; examination will include the entire skin. For each skin lesion observed, the dimensions and location on the body will be recorded. Existing lesions will be monitored throughout the study and changes to the lesions should be recorded in the CRF. Lesions developing during therapy that are suspected keratoacanthomas or squamous cell carcinomas will be biopsied and adequately treated; other lesions may be biopsied per the discretion of the investigator/dermatologist.

7.4.17 Dermatological Photographs

All patients will have dermatological photographs taken at Screening to document any pretreatment skin lesions. Any patient with new or changing skin lesions during the course of treatment will have repeat photographs taken to document the lesion. Refer to the Study Manual for further details.

7.4.18 Pharmacokinetic Measurements

The primary objective of all PK sampling in this study (plasma and urine) is to measure concentrations of MLN2480. A validated liquid chromatography/mass spectroscopy method will be used to quantify concentrations of MLN2480 in plasma and urine. However, pending technical feasibility, these plasma and/or urine samples may additionally be used for exploratory analysis of MLN2480 metabolites to further understand the pathways of metabolism/excretion of MLN2480.

Plasma samples will be collected predose and at prespecified time points following administration of MLN2480 in the dose escalation cohorts, dose expansion cohorts, and the PK expansion cohort. Urine samples will be collected predose and at prespecified time points postdose in the dose escalation cohorts and the PK expansion cohort to estimate the extent of renal excretion of MLN2480.

The predose urine sample on Cycle 1, Day 1 will represent a single void collected before the start of the Day 1 dose. The exact date and time of collection should be recorded.

The postdose urine collection (on Cycle 1, Day 21[Q2D] or Day 22 [QW]) will include all voids collected from 0 to 8 hours after the dose. The patient should be instructed to empty their bladder prior to dosing; this predose void should be discarded unless needed for non-PK purposes. The final urine void of the postdose urine collection should be collected prior to the blood sample for plasma PK scheduled at 8 hours after the dose. The exact date, start and stop times, and total volume of the postdose urine collection should be recorded.

Refer to Table 1-1, Table 1-4, and Table 1-7 for the timing of blood samples for PK assessments in the Q2D Dose Escalation phase, the Q2D PK Expansion cohort, and the Q2D melanoma expansion cohorts, respectively. Refer to Table 1-2 and Table 1-5 for the timing of urine samples for PK assessments in the Q2D Dose Escalation phase and the Q2D PK Expansion cohort, respectively. Refer to Table 1-8, Table 1-9, and Table 1-10 for the timing of blood samples for PK assessments in the QW Dose Escalation and Dose Expansion phases. Refer to Table 1-11 for the timing of urine samples for PK assessments in the QW Dose Escalation phase.

In addition to the scheduled PK sample collections, a blood sample to measure MLN2480 plasma concentrations 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. The date and exact time of the unscheduled sample collection should be recorded, along with the date and exact time of dosing prior to the unscheduled sample collection.

Although the number of PK samples will not be increased, the timing of PK samples may be modified during the study conduct based on preliminary results from interim PK analyses performed during the study or in response to modifications of the dosing schedule.

The dates and exact times of dosing and all PK sample collections will be recorded in the eCRF based on site source documentation.

Details regarding the collection, processing, storage, handling, and shipping of the PK samples are provided in the Laboratory Manual.

7.4.19 Pharmacodynamic Assessment/ Fresh Tumor Biopsies

CCI

[redacted]

CCI

[redacted]

7.4.20 Archival/ Fresh Tumor Specimen Measurements for Tumor Genotyping

CCI

[redacted]

7.4.21 Pharmacogenomic Assessment

CCI

[redacted]

7.5 Completion of Study

Patients will be considered to have completed the study if they complete up to 12 months of treatment with MLN2480 or if they experience disease progression.

Once study drug has been discontinued, all study procedures outlined for the End of Treatment visit will be completed as specified in the Q2D Schedules of Events or the QW Schedules of Events.

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 be withdrawn from the study for any of the following reasons:

- AE
- CR
- Completed maximum number of cycles per protocol
- Lost to follow-up
- Progressive disease (PD)

- Protocol violation
- Symptomatic deterioration
- Unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by patient
- Other

At the time of study drug discontinuation, all study procedures outlined for the End of Study visit will be completed. The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who are withdrawn from study treatment during Cycle 1 for reasons other than DLT will be replaced in the Dose Escalation phase of the study.

7.7 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

This study is noncomparative in nature, ie, formal statistical comparisons will not be performed. Summary tabulations will be presented that will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. A formal statistical analysis plan will be developed and finalized before database lock.

In the Dose Escalation phase, statistical analyses will be primarily descriptive and graphical in nature. In the Dose Expansion phase, ORR in the response-evaluable population will be tabulated descriptively for each cohort and total melanoma expansion cohort (Cohorts 1-6); 95% exact binomial confidence intervals will be provided for the total melanoma expansion cohort. Time-to-event data for the total melanoma expansion cohort will be analyzed by the Kaplan-Meier method and results will be summarized by 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as the percentage of censored observations.

8.1.1 Determination of Sample Size

The total sample size for the study will be approximately 198 patients (approximately 54 patients in the Dose Escalation phases (Q2D and QW) and approximately 144 patients in the Dose Expansion phase [Q2D and QW]). In the Dose Escalation phase, a 3 + 3 dose escalation design will be used; therefore, the sample size is dependent on the number of dose escalation steps and the number of patients per cohort. To further evaluate the safety and preliminary antitumor activity of the selected MLN2480 dose for the Dose Expansion phase, approximately 128 patients with locally advanced metastatic, and/or unresectable melanoma (each cohort will have a maximum of 16 evaluable patients), and 16 patients with advanced solid tumors (excluding lymphoma) will be enrolled in the Dose Expansion phase (Q2D and QW).

8.1.2 Randomization and Stratification

Randomization will not be used in this study; however, patients will be assigned to 1 of 8 expansion cohorts based on tumor type, mutational status, and/or treatment history (see Section 5.1). No stratification is planned for this study. An interactive voice response system will be used for cohort management. Refer to the Study Manual for details.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: The safety population is defined as all patients who receive any amount of MLN2480. This population will be used for all safety analyses, as well as pharmacogenomic analyses.

- DLT-evaluable population: The DLT-evaluable population is defined as all patients in the Dose Escalation phase of the study who either experience DLT during Cycle 1 or complete at least 75% of the planned doses of MLN2480 and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. This population will be used for analysis of MTD.

- Response-evaluable population: The response-evaluable population is defined as all patients with measurable disease who receive any amount of MLN2480 and have at least 1 postbaseline response assessment. This population will be used for response rate and DOR analyses.

- PK-evaluable population: The PK-evaluable population is defined as all patients who have sufficient dosing data and MLN2480 concentration-time data to permit calculation of MLN2480 PK parameters.

- Pharmacodynamic-evaluable population: The pharmacodynamic-evaluable population is defined as all patients who have sufficient dosing data and available pharmacodynamic data. The patients to be included in pharmacodynamic analysis populations will be determined by the sponsor upon review of the data.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

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

8.1.5 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, sex, race, ethnicity, height, weight, and baseline disease characteristics.

8.1.6 Efficacy Analysis

There will be no planned statistical comparisons for efficacy endpoints between dose cohorts in the Dose Escalation phase.

Overall response rate (ORR) is defined as the number of CR and PR in the response-evaluable population. In the Dose Escalation phase, ORR will be tabulated descriptively for each dose group and total. In the Dose Expansion phase, ORR in the response-evaluable population will be tabulated descriptively for each cohort and total dose expansion cohort (Cohorts 1-6, 8, and 9); 95% exact binomial confidence intervals will be provided for the total dose expansion cohort. CR, PR, SD, and PD will also be summarized and analyzed in the same way.

Duration of response (DOR) is defined as the time from the date of first documentation of a response to the date of first documented PD. In the Dose Escalation phase, DOR will be summarized descriptively for each dose group and total. In the Dose Expansion phase, DOR in the response-evaluable population will be summarized descriptively for each cohort and total dose expansion cohort (Cohorts 1-6, 8, and 9).

Progression-free survival (PFS) is defined as the time from the date of first study drug administration to the date of first documented PD or death due to any cause, whichever occurs first. PFS for the total dose expansion cohort will be analyzed by the Kaplan-Meier method, and results will be summarized by 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals, as well as the percentage of censored observations. PFS will be summarized in total for the safety population based on the Kaplan-Meier life test method.

8.1.7 Pharmacokinetic Analysis

MLN2480 PK analyses will be performed on data from the PK-evaluable population.

- PK evaluations from plasma samples collected in the Dose Escalation phase and the PK Expansion cohort will enable calculation of PK parameters, including, but not limited to, C_{max}, C_{trough}, $t_{1/2}$, t_{max}, AUC, apparent oral clearance, peak-to-trough ratio, and accumulation ratio.

- PK evaluation from limited sampling in the melanoma-specific expansion cohorts will contribute to population PK analysis.

- PK evaluations from urine samples collected in the Dose Escalation phase and the PK Expansion cohort will enable calculation of MLN2480 renal clearance and percent dose excreted in urine.

The following analyses will be performed for all patients in the PK-evaluable population:

- Plasma concentrations of MLN2480 will be summarized by time postdose, grouped by dose group and dosing cycle and day. Mean and individual plasma concentration-time profiles will be plotted by dose group and dosing cycle and day.

- PK parameters will be calculated for MLN2480 by noncompartmental analysis as permitted by the data. These parameters will include C_{max}, T_{max}, trough concentration (C_{trough}), $AUC_{0-\tau}$, apparent oral clearance, renal clearance, half life, peak-to-trough ratio, and accumulation ratio. As appropriate, these parameters will be summarized by dose group and dosing cycle and day. Dose proportionality of C_{max} and $AUC_{0-\tau}$ may be assessed graphically and by regression analysis using a power model.

Pharmacokinetic Modeling

MLN2480 PK data collected in this study, together with PK data collected from future studies, may contribute to population PK analysis. The objectives of this analysis are to understand potential sources of PK variation, including patient-specific covariates (eg, age, gender, renal and hepatic function), and to enable exploratory analysis of the relationships between PK and drug effects, including pharmacodynamics, clinical response, and safety. If population PK analysis is considered feasible, the specifics of the modeling approaches will be described separately in a population PK analysis plan, and the results will be reported separately.

8.1.8 Pharmacodynamic Analysis

CCI

[redacted]

CCI

[redacted]

8.1.9 Pharmacogenomic Analysis

CCI

[redacted]

8.1.10 Safety Analysis

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

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) for the purpose of summarization. All AEs occurring on study will be listed in data listings. Treatment-emergent adverse events that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated. Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs Drug-related treatment-emergent AEs

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

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

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients in the safety population) will be tabulated in each dose group and total for dose escalation phase, as well as each cohort and total for the dose expansion phase by the MedDRA preferred term. Tabulation also will be provided that enumerates AEs by maximum intensity. Deaths, SAEs, and AEs resulting in study drug discontinuation will be tabulated.

Clinical laboratory parameters will be summarized at each scheduled time point in the Dose Escalation phase, as well as each cohort and total for the Dose Expansion phase. Shift tables will be produced for selected laboratory parameters. These tables will summarize the number of patients with each baseline NCI CTCAE grade and changes to the worst NCI CTCAE grade during study.

Descriptive statistics for the actual values of vital signs and weight over time will be tabulated for Dose Escalation phase, as well as each cohort and total for the Dose Expansion phase by scheduled time point.

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

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

ECG Analysis

A summary of ECG abnormalities will be presented by visit for the dose escalation phase, as well as each cohort and total for the dose expansion phase. The ECG intervals (QT, QT

adjusted by an appropriate correction [QTcB (Bazzett) and QTcF], PR, QRS, and RR) and HR will be summarized by dose cohort (and gender, if deemed appropriate) at each scheduled time point, along with change from baseline to each posttreatment time point.

The effects of MLN2480 on select ECG parameters (eg, QTc) may be evaluated using data from this and other studies using a population concentration-effect analysis approach. If conducted, this analysis will be reported separately.

8.1.11 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 patient 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 means any untoward medical occurrence in a patient or patient 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 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.[37] Clarification should be made between an 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 leukocyte count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

9.1.4 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the investigator between the patient's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

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. When patients have been in the study for 4 years or longer, nonserious AEs will no longer be recorded.

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 Cognizant, the designees of Millennium Pharmacovigilance, for SAE reporting (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 Cognizant or Millennium. Serious adverse event report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

Cognizant (US and Canada)

Toll-Free Fax#: 1-800-963-6290

Email: takedaoncocases@cognizant.com

Cognizant (All other countries [Rest of World])

Fax#: 1-202-315-3560

Email: takedaoncocases@cognizant.com

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 the patient signed the ICF are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (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. 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

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

- AEs will be reported from the start of 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. When patients have been in the study for 4 years or longer, nonserious AEs will no longer be reported.

- Serious pretreatment events will be reported to Cognizant (see Section 9.2) 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 Cognizant from the start of the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. All 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 Cognizant (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 Cognizant (see Section 9.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10. ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

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

10.2 Data Quality Assurance

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

Project clinicians 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.

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

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

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

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

10.4 Study Monitoring

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

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

10.5 Ethical Considerations

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

10.6 Patient Information and Informed Consent

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

10.7 Patient Confidentiality

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

10.8 Investigator Compliance

The investigator will conduct the study 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 study 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 the Medical Information Call Center (Dohmen Life Science Services [DLSS]) (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

For Product Complaints,
For more information call 1-844-ONC-TKDA (1-844-662-8532)
or email GlobalOncologyMedinfo@takeda.com

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

10.12 Closure of the Study

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

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

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written

notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

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

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

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

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

10.13 Record Retention

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

11. USE OF INFORMATION

All information regarding MLN2480 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 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 study results pursuant to the terms contained in the applicable Clinical Trial Agreement.

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

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

- If patentable patient matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Millennium's receipt of the proposed publication to allow time for the filing of patent applications covering patentable patient matter.
- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Millennium's request.

The overall principal investigator will be the last author on abstracts and publications of the data generated from this study. Other authors will be listed according to number of patients enrolled to the study. If the principal investigator has the highest enrollment, he/she may

choose to be either first or last author. This policy may be changed with the agreement of both the investigators and Millennium.

12. INVESTIGATOR AGREEMENT

I have read Protocol C28001 Amendment 8: An Open-Label, Phase 1, Dose Escalation Study of MLN2480 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients With Metastatic Melanoma. I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

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

13. REFERENCES

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3. Avruch J. MAP kinase pathways: the first twenty years. Biochim Biophys Acta 2007;1773(8):1150-60.
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14. APPENDICES

14.1 Eastern Cooperative Oncology Group Scale for Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[39]

14.2 22-Day Treatment Cycle Schedule of Events Tables

The study cycle length was extended from 22 days to 28 days upon implementation of Protocol Amendment 3. For reference and clarity, this appendix contains the 22-Day Treatment Cycle Schedule of Events Tables. The 28-day Treatment Cycle Schedule of Events Tables are located in the body of the protocol.

22-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21		
	≤ 21 days Prior to Day 1	Predose	Postdose	Day 2	Day 3	Day 9	Day 15	Predose	Postdose	Day 22
Informed consent form	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Complete physical examination, height, and body weight measurement	X	X[a]								
Dermatological examination with documentation of any suspicious lesions[b]	X	X				X	X			X[c]
12-lead ECG[d]	X	X	X		X			X	X	
Vital signs (temperature, blood pressure, pulse rate)[e]	X	X[f]	X[f]			X[f]	X[f]			
ECOG performance status	X	X[a]								
Laboratory tests										
Hematology[g]	X	X[a, h]				X	X			
Blood chemistry[i]	X	X[a, h]				X	X			
Bone marrow aspirate and biopsy[j]										
Optional tumor biopsy[k]	X								X	
Coagulation[l]										
Thyroid function	X									
Serum pregnancy test (female patients of reproductive potential)	X[a]	X[a]								

22-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21		
	≤ 21 days Prior to Day 1	Predose	Postdose	Day 2	Day 3	Day 9	Day 15	Predose	Postdose	Day 22
Urinalysis[m]	X	X[a]								
Serum samples for biomarker assessment		X[n]							X[o]	
Blood sample for pharmacogenomic assessment (germline DNA)		X								
Blood sample for PK assessment (Dose Escalation phase)[p, q]		X	X	X	X	X	X	X	X	X
Urine samples for PK assessment (Dose Escalation phase)[r]		X							X	
Confirmation of available FFPE tumor tissue[s]	X									
Disease assessment, including CT or MRI scan	X[t]									
Concomitant therapy and procedures recording[u]		Concomitant therapy and procedures must be recorded from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever comes first.								
AE reporting		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								
	SAEs[v] will be collected from signing of the informed consent form through 30 days after the last dose of study drug.									
MLN2480 administration (Dose Escalation phase only)[w]		MLN2480 dosing is once every 2 days on Days 1-21 of a 22 day cycle (11 doses), starting on Day 1								

Abbreviations: aPTT=activated partial thromboplastin time; AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRF=Case Report Form; CT=computed tomography; DLT=dose-limiting toxicity; ECG=Electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed paraffin-embedded; ICF=informed consent form;

22-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21		
	≤ 21 days Prior to Day 1	Predose	Postdose	Day 2	Day 3	Day 9	Day 15	Predose	Postdose	Day 22

MRI=magnetic resonance imaging; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; SAE=serious adverse event; WBC=white blood cell.

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 22).

a Assessments need not be repeated if Screening assessments were performed within 72 hours before MLN2480 dosing, unless otherwise specified. Height is to be collected at Screening only.

b All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. The examination for skin lesions will include the entire skin. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

c Assessment will be performed on Cycle 1, Day 22 ± 5 days.

d A single 12-lead ECG will be collected at Screening to assess eligibility. Subsequent ECGs will be collected in triplicate at all time points. The triplicate ECG measurements should be completed after a 5-minute rest period in the supine position and will be recorded at 2 to 5 minute intervals immediately before the corresponding PK blood draw. The triplicate ECGs will be collected predose on Day 1 (within 1 hour prior to dosing) and on Days 1 and 21 at 2, 4, and 6 hours after dosing. Triplicate ECGs will also be collected 48 hours post Day 1 dose (predose within 1 hour prior to Day 3 dosing).

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

f On Days 1, 9, and 15 vital sign measurements will be performed within 15 minutes prior to dosing. On Cycle 1, Day 1 only, also perform vital sign measurements at 2 hours ± 10 minutes and 6 hours ± 10 minutes postdose.

g Hematology will be tested at local laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 > 1,000/μL and platelet counts return to > 50,000/μL.

h Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts [only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion], absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle.

i Blood chemistry results will include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

j Bone marrow aspirate and biopsy will be encouraged only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

22-Day Treatment Cycle: Cycle 1 Schedule

	Screening	Day 1						Day 21		
	≤ 21 days Prior to Day 1	Predose	Postdose	Day 2	Day 3	Day 9	Day 15	Predose	Postdose	Day 22

k Biopsy of tumor will be performed at Screening and 3 to 12 hours after MLN2480 dosing on Cycle 1, Day 21.

l Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be > 75,000/mm^3.

m Urinalysis includes dipstick for blood, protein, and glucose (microscopic examination, if abnormal). Samples will be collected predose.

n Predose plasma sample will be taken within 1 hour prior to MLN2480 dosing.

o Postdose plasma samples for biomarker analysis will be taken 4 and 48 hours following MLN2480 dosing. (The 48-hour postdose sample corresponds to the Cycle 2, Day 1 predose sample.)

p Refer to Table 1-1 for details on assessment time points. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

q In addition to the scheduled PK sample collections, a blood sample to measure MLN2480 plasma concentrations 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

r Refer to Table 1-2 for details on collection time points. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of urine PK samples.

s FFPE tumor tissue or slides from the diagnostic biopsy or surgical specimen from the most recent diagnosis, or FFPE tumor tissue from a new biopsy if archival tumor tissue is unavailable or inadequate.

t Refer to Section 7.4.15 and Section 14.3.

u Concomitant therapies and procedures must be recorded from Screening through the End of Study visit or the start of subsequent antineoplastic therapy, whichever comes first.

v Including serious pretreatment events; see Section 9.

w Patients will take MLN2480 orally once every 2 days and will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose. On dosing days when the patient does not have a clinic visit (ie, Days 5, 7, 11, 13, 17, and 19), patients will take their dose of MLN2480 at home.

22-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 22)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 9 ± 2 Days**	**Day 21 ± 2Days**
Physical examination and body weight measurement	X		
Dermatological examination with documentation of any suspicious lesions[a]	X		X
12-lead ECG[b]	X		
Vital signs (temperature, blood pressure, pulse rate)[c]	X	X	
Laboratory tests			
Hematology[d]	X[e]	X	
Blood chemistry[f]	X[e]	X	
Bone marrow aspirate and biopsy[g]			
Coagulation[h]			
Thyroid function	X		
Urinalysis[i]	X		
Serum samples for biomarker assessment	X[j]		
Blood samples for PK assessment (Dose Escalation phase)	X[k, l]		
Disease assessment, including CT or MRI scan			X[m]
Concomitant therapy and procedures recording[n]	X	X	X
AE reporting	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first.		
	SAEs will be collected from signing of the informed consent form through 30 days after the last dose of study drug.[o]		
MLN2480 administration (Dose Escalation phase only)[p]	MLN2480 dosing is once every 2 days on Days 1-21 of a 22 day cycle (11 doses), starting on Day 1		

Abbreviations: aPTT=activated partial thromboplastin time; AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CT=computed tomography; ECG=Electrocardiogram; ECOG=Eastern Cooperative Oncology

22-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 22)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 9 ± 2 Days**	**Day 21 ± 2Days**

Group; MRI=magnetic resonance imaging; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WBC=white blood cell.

a All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. The examination for skin lesions will include the entire skin. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

b The triplicate ECG measurements should be completed after a 5-minute rest period in the supine position and will be recorded at 2 to 5 minute intervals immediately before the corresponding PK blood draw. The triplicate ECGs will be collected predose (within 1 hour prior to dosing).

c Perform vital signs measurement within 15 minutes prior to dosing. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d Hematology will be tested at local and central laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 > 1,000/µL and platelet counts return to > 50,000/µL.

e Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts, absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle. Hematology and blood chemistry for Cycle 2, Day 1 may be completed up to 72 hours prior to Day 1.

f Blood chemistries will be tested at local laboratories and include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

g Bone marrow aspirate and biopsy will be encouraged for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

h Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be >75,000/mm^3.

i Urinalysis includes dipstick for blood, protein, and glucose (microscopic examination, if abnormal). Samples will be collected predose.

j This serum biomarker sample corresponds to the Cycle 1, Day 21, 48-hour postdose biomarker sample. It will be collected within 1 hour prior to MLN2480 dosing on Cycle 2, Day 1.

k Refer to Table 1-1 for details on assessment time points. Refer to Laboratory Manual for details on collection, processing, storage, and shipment of plasma PK samples.

l In addition to the scheduled PK sample collections, a blood sample to measure MLN2480 plasma concentrations 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

22-Day Treatment Cycle: Cycle 2 Schedule			
	Cycle 2 (Day 1 through Day 22)		
Tests and Assessments	**Day 1 ± 2 Days**	**Day 9 ± 2 Days**	**Day 21 ± 2Days**

Section 7.4.18

m Disease assessments (including CT or MRI scans of all sites of disease) will be performed every 2 cycles after starting MLN2480 treatment, beginning on Cycle 2, Day 21 ± 2 days. Imaging and assessment may be conducted up to 3 days in advance of Day 21 (ie, Days 18 to 21). Any complete response or partial response must be confirmed at least 4 weeks after the response is first documented. Clinical response and disease progression will be evaluated using RECIST, version 1.1, per investigator assessment.

n Concomitant therapies and procedures must be recorded from Screening through the End of Study visit or until the start of subsequent antineoplastic therapy, whichever occurs first.

o Including serious pretreatment events; see Section 9.

p Patients will take MLN2480 orally once every 2 days and will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose. On dosing days when the patient does not have a clinic visit (ie, Days 3, 5, 7, 11, 13, 15, 17, and 19), patients will take their dose of MLN2480 at home

22-Day Treatment Cycle: Cycle 3 and Subsequent Cycles				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 22 ± 2 Days)			
Tests and Assessments	**Day 1**	**Day 9**	**Day 21**	**End of Study Visit[a]**
Physical examination and body weight measurement	X			X
Dermatological examination with documentation of any suspicious lesions[b]			X	X
Single 12-Lead ECG[c]	X			X
Vital signs (temperature, blood pressure, pulse rate)[d]	X	X		X
ECOG performance Status				X
Laboratory tests				
Hematology[e]	X[f]	X		X
Blood chemistry[g]	X[f]	X		X
Bone marrow aspirate and biopsy[h]				
Coagulation[i]				
Thyroid function	X			X
Serum pregnancy test (female patients of reproductive potential)				X
Urinalysis[j]	X			X
Disease assessment, including CT or MRI scan			X[k]	X[l]
Serum samples for biomarker assessment	X[m]			X
Concomitant therapy and procedures recording[n]	X	X	X	X
AE reporting	AEs will be recorded from first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first.			
	SAEs will be collected from signing of the informed consent form through 30 days after the last dose of study drug[o]			
MLN2480 administration (Dose Escalation phase only)[p]	MLN2480 dosing is once every 2 days on Days 1-21 of a 22 day cycle (11			

22-Day Treatment Cycle: Cycle 3 and Subsequent Cycles				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 22 ± 2 Days)			
Tests and Assessments	**Day 1**	**Day 9**	**Day 21**	**End of Study Visit[a]**
	doses), starting on Day 1			

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=Absolute Neutrophil Count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRF=case report form; CT=computed tomography; ECG=Electrocardiogram; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WBC=white blood cell

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. Patients who discontinue study treatment early should complete the End of Study visit 30 (+10) days after the last dose of study treatment.

b All patients will be assessed by the investigator or a consulting dermatologist at the visits specified. The examination for skin lesions will include the entire skin. Existing lesions will be monitored throughout the study and changes to the lesions will be recorded in the CRF. For lesions developing during treatment that are suspected keratoacanthomas or squamous cell carcinomas, the dimensions and location on the body will be recorded in the CRF and they will be subsequently biopsied/adequately treated. Other lesions that develop during treatment should be recorded on the AE form and may be biopsied at the discretion of the investigator/ dermatologist.

c A single 12-lead ECG will be collected predose on Day 1 and the EOS visit. When the timing of a blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

d Predose (within 15 minutes prior to dosing; except at End of Study visit where no study drug is administered). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

e Hematology will be tested at local laboratories and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts (only for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion), absolute differential, and ANC. 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 > 1,000/μL and platelet counts return to > 50,000/μL.

f Hematology results (including hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts, absolute differential, and ANC) and blood chemistry results (including creatinine, total bilirubin, AST, and ALT) will be evaluated before the patient is allowed to take their dose of MLN2480 on Day 1 of each cycle. Hematology and blood chemistry for Cycle 3 and subsequent cycles Day 1 may be completed up to 72 hours prior to Day 1.

g Blood chemistry results include glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT, albumin, and calcium.

h Bone marrow aspirate and biopsy will be encouraged for patients who experience recurrent anemia with hemoglobin < 9 g/dL, despite blood transfusion.

i Within 48 hours of any invasive procedure (ie, tumor biopsy or bone marrow biopsy), aPTT and PT must be within the normal range. For tumor and bone marrow biopsies, platelet count should be >75,000/mm^3.

j Urinalysis includes dipstick for blood, protein, and glucose (microscopic examination, if abnormal). Samples will be collected predose.

22-Day Treatment Cycle: Cycle 3 and Subsequent Cycles				
	Cycle 3 and Subsequent Cycles (Day 1 through Day 22 ± 2 Days)			
Tests and Assessments	**Day 1**	**Day 9**	**Day 21**	**End of Study Visit[a]**

k Disease assessments (including CT or MRI scans of all sites of disease) will be performed every 6 weeks ± 2 days after starting MLN2480 treatment, beginning on Cycle 2, Day 21 ± 2 days. Imaging and assessment may be conducted up to 3 days in advance of Day 21 (ie, Days 18 to 21). Any complete response or partial response must be confirmed at least 4 weeks after the response is first documented. Clinical response and disease progression will be evaluated using RECIST, version 1.1 (see Section 14.3), per investigator assessment.

l Disease assessments need not be repeated if performed within 4 weeks prior to the End of Study visit.

m On Cycle 3, Day 1 ± 2 days, and beyond, the predose serum sample will be taken within 1 hour prior to MLN2480 dosing.

n Concomitant therapies and procedures must be recorded from Screening through the End of Study visit or until the start of subsequent antineoplastic therapy, whichever occurs first.

o Including serious pretreatment events; see Section 9.

p Patients will take MLN2480 orally once every 2 days and will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose. On dosing days when the patient does not have a clinic visit (ie, Days 3, 5, 7, 11, 13, 15, 17, and 19), patients will take their dose of MLN2480 at home.

14.3 Response Evaluation Criteria in Solid Tumors (Version 1.1)

All sites of disease, target and nontarget lesions must be assessed at Baseline. Objective disease status is to be recorded at each evaluation using the response categories and definitions provided in this section.

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at Baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for reproducible repeated measurements. Measurements must be provided for target measurable lesions.

Confirmation of response is not required, as response is not the primary endpoint of this study.

Disease Response Criteria for Target and Nontarget Lesions

Evaluation of target lesions	
Complete Response:	Disappearance of all target lesions
Partial Response:	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease:	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Evaluation of nontarget lesions	
Complete Response:	Disappearance of all nontarget lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease:	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease:	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[40]

Abbreviation: LD=longest diameter.

The following table summarizes the overall response status calculation at each time point for patients who have measurable disease per RECIST at baseline.

Time Point Response: Patients With Target (± Nontarget) Disease

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

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[40]

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

The following table summarizes the overall response status calculation at each time point for patients who have nonmeasurable (therefore nontarget) disease at baseline.

Time Point Response: Patients With Nontarget Disease Only

Nontarget lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease.

14.4 Amendment 1 Summary of Changes

Rationale for Amendment 1

The primary purpose for this amendment is to shorten the time period during which urine is collected for postdose pharmacokinetic (PK) assessments of MLN2480 in the dose escalation phase. The originally planned 48-hour urine collection period after the Cycle 1, Day 21 dose will be shortened to an 8-hour urine collection period after the Cycle 1, Day 21 dose. In order to ensure accurate quantitation of MLN2480 concentrations and determination of renal clearance, a detergent (3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate [CHAPS]) must be added to each urine void to prevent nonspecific binding of MLN2480 to collection containers. It was not considered feasible for patients to add accurate volumes of CHAPS to urine voids collected at home. As a result, the collection period was condensed when patients are already at the study site so that appropriately trained staff can add an accurate volume of CHAPS to each urine void.

In addition to the above purpose for this amendment, skin punch biopsies will not be performed in this study and clarification has been added indicating that core or excisional biopsies are acceptable. Footnotes in the Schedules of Events were clarified. Section 7 was harmonized with the Schedules of Events and AE reporting language in the Schedules of Events was aligned with that in Section 9 and according to Millennium template standards. Nonclinical PK experience was updated to reflect content in Addendum 1 of the Investigator's Brochure (IB) unavailable at the time of the original protocol. The number of study centers was corrected for the Dose Expansion phase. The inclusion criterion was clarified to ensure that patients should have thyroid hormone tests consistent with stable thyroid function and allow patients with stable disease to be enrolled. Clarification was added to specify that based on data from the Dose Escalation phase, patients may be treated at the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) in the Dose Expansion phase. Dose modification language was expanded to allow more conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level for patient safety or a better understanding of the study drug. Reference to "Directions for Use" (as a standalone document) has been removed from the protocol as instructions for handling and administration of MLN2480 are contained in the Pharmacy Manual and handling of PK samples is in the Laboratory Manual. Instructions for dispensation and unused study drug destruction policies were clarified. Patient information will be captured and managed by study sites by Inform. Electrocardiogram (ECG) instructions were clarified and the time window for predose ECG was increased from 30 minutes to 1 hour for all treatment cycles. Additional details for collection of blood and urine samples for PK analysis were specified and an option for unscheduled blood sample collection for plasma PK analysis at the time of a serious or unusual adverse event (AE) was added. Examples of cytochrome P_{450} (CYP) enzymes, which may be included in the pharmacogenomics assessment, were added. Serious pretreatment events will be reported to PPDI Pharmacovigilance. Administrative changes include, but are not limited to, updating the cover page with current signatories and assigning table numbers.

Purposes for Amendment 1

The purposes of this amendment are to:

- Update the cover page with current signatories
- Align AE reporting language in the Schedules of Events and in Section 9 with the Millennium template standards
- Clarify footnotes for vital sign measurements in the Schedules of Events and specify that blood pressure should be determined with the patient in a seated position after sitting quietly for 5 minutes
- Remove the option to perform skin punch biopsies, clarify that core or excisional biopsies are allowed, and delete reference to the Study manual in the Schedules of Events.
- Clarify that the 48-hour postdose serum sample for biomarker analysis corresponds to the Cycle 2, Day 1 predose sample
- Clarify that hematology and blood chemistry may be completed up to 72 hours prior to Day 1 to allow time for review of results prior to initiating another cycle according to the Schedules of Events
- Align the Schedules of Events with Section 7.4.15 indicating that imaging and assessment may be conducted up to 3 days in advance of Day 21 (ie, Days 18 to 21)
- Remove time window and clarify timing for single 12-lead ECGs for Treatment Cycle 3 and Subsequent Cycles in the Schedules of Events
- Assign numbers to the supplemental Schedules of Events tables for Plasma Pharmacokinetic Assessment Time Points (Dose Escalation and Dose Expansion phases), provide time windows, and additional clarification for blood sample collection
- Shorten the time period during which urine is collected for postdose PK assessments (Dose Escalation phase only) from a 48-hour to an 8-hour collection period after the Cycle 1, Day 21 dose, assign a number to the supplemental Schedule of Events table for Urine Samples for Pharmacokinetic Assessments, and provide additional clarification for urine sample collection
- Align the nonclinical pharmacokinetics experience section with Addendum 1 of the IB unavailable at the time of protocol development
- Clarify replacement procedures for patients discontinuing study treatment for reasons other than MLN2480-related toxicity
- Correct the number of study centers from approximately 7 to 12 to approximately 8 to 13 US and international sites for the Dose Expansion phase
- Clarify that patients must return to the study site 30 days after administration of the last dose of study drug to complete the End of Study visit procedures
- Clarify the inclusion criterion to ensure that patients have thyroid hormone tests consistent with stable thyroid function and that patients on a stable dose of thyroid replacement therapy are eligible. Additionally, remove reference to specific thyroid function tests as these are standard practice
- Clarify that once the MTD has been identified, additional patients may be treated at the

MTD or at the RP2D in the Dose Expansion phase

- Expand dose modification language to allow more conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level for patient safety or a better understanding of MLN2480
- As there is no long-term follow up in this study, after the End of Study visit, concomitant therapies and procedures or treatment of ongoing AEs will not be recorded
- Remove reference to a specific "Directions for Use" document for instructions on handling, preparation, administration, and disposal of the study treatment; and refer study site staff to the Pharmacy Manual
- Clarify instructions for dispensation of study drug
- Remove reference to a specific "Directions for Use" document for instructions on study treatment storage and refer study sites to the Pharmacy Manual
- Clarify unused study drug destruction policies
- Clarify that patient information will be captured and managed by study sites on electronic case report forms by Inform
- Harmonize Section 7.4.8 with the Schedules of Events for the timing of serum pregnancy tests to be obtained for women of childbearing potential
- Clarify time points for single ECG collection, update instructions for the collection of triplicate ECGs, and increase the time window for predose ECG assessments (single and triplicate) from 30 minutes to 1 hour for all treatment cycles and align the Schedules of Events with Section 7.4.13
- Remove reference to the Study Manual for details regarding handling and shipping of the clinical laboratory samples since they are performed locally
- Harmonize Section 7.4.14 with the Schedules of Events for absolute reticulocyte count
- Clarify that PK samples for plasma and urine will be taken at prespecified time points predose and postdose
- Provide the option for unscheduled PK blood sample collection at the time of a serious or unusual AE
- Clarify that the number of PK samples will not be increased and that the timing of PK samples may be modified during the study conduct based on preliminary study results
- Specify that the dates and times of dosing and PK sample collection will be recorded in the eCRF
- Remove reference to the Study Manual for details regarding the collection, processing, storage, handling, and shipping of the PK samples, which are provided in the Laboratory Manual
- Remove reference to the Pharmacy Manual for instructions on the pharmacodynamic assessment
- Clarify that pharmacodynamic assessment includes tumor biopsies and specify that core and excision biopsies are acceptable
- Provide specific examples of CYP enzymes known to exhibit genetic variation for potential pharmacogenomics assessment

- Specify that serious pretreatment events will be reported to PPDI Pharmacovigilance
- Correct typographical errors, punctuation, grammar, abbreviations, and formatting

14.5 Amendment 2 Summary of Changes

Rationale for Amendment 2

The primary purpose for this amendment is to increase the frequency of dermatological examinations during the course of the study. Patients have presented with unexpected hyperpigmented lesions in Cycle 1 that differ from the expected keratoacanthomas or squamous cell carcinomas that may occur due to MLN2480's mechanism of action. Although the lesions do not appear malignant at this time, additional monitoring for safety purposes will help to capture the onset and development of these hyperpigmented lesions. In addition, language allowing for the investigator/dermatologist's discretion as whether to biopsy skin lesions that are not suspected keratoacanthomas or squamous cell carcinomas has been added.

Other updates to the study have been made, per the sponsor's current practices.

Purposes for Amendment 2

The purposes of this amendment are to:

- Update the cover page with current signatories
- Clarify dermatological exam procedures and add exams to the following study visits:
    - Cycle 1: Day 1 (predose), Day 9, Day 15
    - Cycle 2: Day 1, Day 22
    - Cycle 3 and beyond: Day 21 (will coincide every third cycle with the dermatological exam already in the protocol)
- Allow for investigator/dermatologist discretion as whether to biopsy skin lesions that are not suspected keratoacanthomas or squamous cell carcinomas
- Replace the term medical monitor with project clinician to align with current company standards
- Clarify that assessments to be performed at the End of Treatment visit are listed in the Schedule of Events
- Update AE evaluation and analysis language, and clarify tables and listings of TEAEs to be provided
- Delete redundant serious adverse event reporting language
- Update language to current company standards and remove text regarding the start of antineoplastic or anticancer therapy as it relates to follow-up of AEs
- Remove requirement to report medication errors to MedComm Solutions to reflect the sponsor's current practices
- Correct typographical errors, punctuation, grammar, abbreviations, and formatting

14.6 Amendment 3 Summary of Changes

Rationale for Amendment 3

The primary purposes for this amendment are to revise the details of the Dose Expansion phase of the study and to redefine the length of the dosing cycle from Q2D for 22 days to Q2D for 28 days.

It is hypothesized that tumor genotype and treatment history may serve as a predictor of response for patients with melanoma, and 6 unique melanoma cohorts were added to the Dose Expansion phase to contextualize safety and preliminary antitumor activity.

- Cohort 1: BRAF mutation-positive melanoma, naïve to prior therapy with vemurafenib, ipilimumab, and investigational RAF and MEK inhibitors
- Cohort 2: BRAF mutation-positive melanoma, which in response to previous treatment with vemurafenib, ipilimumab, or investigational RAF or MEK inhibitors have 1) relapsed following an objective response; 2) failed to demonstrate an objective response; and/or 3) could not tolerate such a regimen due to unacceptable toxicity
- Cohort 3: NRAS mutation-positive melanoma, naïve to prior therapy with ipilimumab and investigational RAF and MEK inhibitors
- Cohort 4: NRAS mutation-positive melanoma, which in response to previous treatment with ipilimumab and investigational RAF and MEK inhibitors have 1) relapsed following an objective response; 2) failed to demonstrate an objective response; and/or 3) could not tolerate such a regimen due to unacceptable toxicity
- Cohort 5: BRAF/NRAS mutation-negative melanoma (wild type), naïve to any prior anticancer therapy
- Cohort 6: BRAF/NRAS mutation-negative melanoma (wild type), who have received at least 1 line of prior anticancer therapy

A seventh expansion cohort, the PK Expansion cohort, in patients with any advanced solid tumor (excluding lymphoma) was added to evaluate safety and preliminary antitumor activity of MLN2480 and further characterize the PK of MLN2480.

This amendment redefines the cycle length for newly enrolling patients in the Dose Escalation phase and all patients in the Dose Expansion phase from 22 days (11 doses) to 28 days (14 doses) to improve clinical feasibility and better facilitate future combination with other drugs. Regardless of the cycle length, MLN2480 is continuously dosed every other day with no treatment-free period at the end of each cycle.

Purposes for Amendment 3

The purposes of this amendment are to:

- Update the cover page with current Global Clinical Lead signatory
- Update the total number of patients in the study to reflect the 7 cohorts added to the Dose Expansion phase
- Add details for 6 melanoma cohorts, based on prospectively analyzed genotype during Screening and treatment history, to the Dose Expansion phase

- Add 1 PK cohort, consisting of patients with any advanced solid tumor (excluding lymphoma), to the Dose Expansion phase and present the modified dosing schedule for cycle 1 of the PK Expansion cohort
- Clarify procedure for collecting tumor biopsies for genotyping and pharmacodynamic marker analysis
- Extend the length of the dosing cycle for this Q2D continuously administered drug from 22 days (11 doses) to 28 days (14 doses)
- Add mandatory digital photographs for all patients at Screening and if any new or changes in skin lesions occur during the study
- Add mandatory tumor biopsies for the melanoma cohorts of the Dose Expansion phase
- Change serum samples to plasma samples for biomarker assessment and collection of circulating tumor DNA
- Update currently approved standard of care therapies for melanoma based on recent approval of ipilimumab and vemurafenib
- Clarify concomitant medications and exclusion criteria based on newly acquired in vitro metabolism information
- Add detail to PK analysis section
- Define the pharmacodynamic population
- Define ECG collection and analysis
- Define the pharmacogenomic analysis
- Define the normal platelet count range and time frame to > 75,000/mm^2 within 48 hours of biopsy
- Increase the number approximate number of study centers in the Expansion phase from 8 to 13, to read 10 to 18.
- Correct typographical errors, punctuation, grammar, and formatting

14.7 Amendment 4 Summary of Changes

Rationale for Amendment 4

The rationale for this amendment is to specify that individual Dose Expansion cohorts may be opened or closed sequentially or in parallel at the sponsor's discretion. In addition, permitted and restricted prior anti-cancer therapies have been revised based on emerging response data. Ipilimumab was removed as an excluded medication for the treatment-naïve cohorts (Cohorts 1 and 3), and anti-PD-1 monoclonal antibodies (mAbs) were added as a restricted type of medication for all the melanoma expansion cohorts (Cohorts 1-6).

Other substantive changes include revising the definition of true abstinence, updating concomitant medications to be used cautiously, and clarifying the SAE reporting window. Clarifications to the study design and minor grammatical changes have also been incorporated.

Purposes for Amendment 4

The purposes of this amendment are to:

- Add anti-PD-1 mAbs to the background section describing current treatment options for melanoma
- Clarify that the MTD and/or RP2D will be determined for the 28-day treatment cycle before starting the Dose Expansion phase
- Specify that individual Dose Expansion cohorts may be opened or closed sequentially or in parallel at the sponsor's discretion, on the basis of emerging data
- Modify the cohort definitions by removing ipilimumab as a restricted anti-cancer therapy for the treatment-naïve melanoma Dose Expansion cohorts (Cohorts 1 and 3) and adding anti-PD-1 mAbs as a restricted anti-cancer therapy for all the melanoma Dose Expansion cohorts (Cohorts 1 through 6)
- Add prior treatment with anti-PD-1 mAbs as an exclusion factor for patients in any of the 6 melanoma Dose Expansion cohorts
- Allow a 72-hour window for performing the dermatological examination
- Correct the frequency of disease assessments
- Clarify that for patients undergoing biopsy procedures, prothrombin time and activated partial thromboplastin time must be within the normal range and platelet count should be > 75,000 within 48 hours before biopsy
- Clarify that genotyping results from a fresh biopsy obtained during Screening are required for assignment of patients to 1 of the 6 melanoma cohorts in the Dose Expansion phase of the study
- Clarify that the effect of MLN2480 CCI [redacted]
- Modify contraception language regarding abstinence
- Update concomitant medications to be used cautiously based on newly learned in vitro drug transporter information
- Correct the storage temperature for MLN2480 tablets
- Update the reporting period for SAEs to Millennium from 1 working day to 24 hours
- Correct typographical errors, punctuation, grammar, and formatting

14.8 Amendment 5 Summary of Changes

Rationale for Amendment 5

The primary rationale for this amendment is to clarify procedures and recommendations related to the Dose Expansion phase of the study. Safety information has been added on the basis of observations thus far in the Dose Escalation phase, as well as known class effects of RAF kinase inhibitors. Modifications include the addition of photosensitivity language to the precautions and restrictions section; the insertion of management guidelines for ocular

disturbances, elevated creatinine kinase, and rash; and the addition of dose modification recommendations.

The definitions of the 6 melanoma expansion cohorts have been modified to clarify permitted and/or restricted prior treatments. Changes include removal of the word 'investigational' from Cohorts 1 through 4 to account for recent or anticipated regulatory agency approvals of RAF or MEK inhibitors, as well as permissibility of prior anti-PD-1 usage in Cohorts 1 through 6 with a ≥ 6-week washout period. The exclusion criterion of prior anti-PD-1 usage has also been deleted.

Other substantive changes include clarifying tumor biopsy procedures for genotyping, expanding the duration of the Screening period from 21 to 28 days, adding the dermatological exam window to the Q2D 28-Day Treatment Cycle: Cycle 1 Schedule of Events table, clarifying that the Cycle 1, Day 1 pregnancy test can be urine or serum, and clarifying the statistical methods of analysis.

The lettering of footnotes in the Q2D 28-Day Treatment Cycle: Cycle 1 Schedule of Events table has been updated to reflect the insertion of pregnancy footnote 'm.'

Other minor clarifications to procedures are captured in the following bullets.

Purposes for Amendment 5

The purposes of this amendment are to:

- Clarify the dermatological exam window in the Q2D 28-Day Treatment Cycle: Cycle 1 Schedule of Events table
- Add background information on other therapeutic agents that have reached late-stage development or approval for the treatment of metastatic melanoma
- Clarify Screening tumor biopsy procedures
- Clarify procedures for enrollment of patients into 1 of the 6 melanoma cohorts on the basis of genotype
- Revise melanoma cohort definitions to remove redundancy and permit anti-PD-1 mAbs
- Modify inclusion criterion to allow prior use of anti-PD-1 mAbs
- Remove exclusion criterion for prior use of anti-PD-1 mAbs
- Clarify dose modification procedures for the Dose Escalation and Dose Expansion phases
- Add photosensitivity to the precautions and restrictions during the study
- Add recommendations for management of clinical events during the Dose Expansion phase
- Add text describing treatment group assignments for the Dose Expansion phase
- Extend the Screening period from 21 to 28 days
- Permit the Cycle 1, Day 1 pregnancy test to be serum or urine
- Correct the assessment window for disease assessments
- Add creatine kinase to the list of blood chemistry assessments
- Clarify PK collection procedures

- Clarify statistical methods of analysis for the Dose Escalation phase and Dose Expansion phase
- Clarify demographic and baseline characteristics to be collected
- Add SAE Reporting contact information for ex-US and Canada
- Correct typographical errors, punctuation, grammar, and formatting

14.9 Amendment 6 Summary of Changes

Rationale for Amendment 6

The purpose of this amendment is to introduce additional dose escalation cohorts that will evaluate the maximum tolerated dose (MTD) of MLN2480 administered on a weekly (QW) dosing schedule for the 28-day treatment cycle. The rationale for evaluation of weekly dosing as an alternate dosing schedule is as follows: Analysis of exposure-efficacy relationships in preclinical mouse xenograft models of tumor growth inhibition indicate that more robust mitogen-activated protein (MAP) kinase pathway inhibition may be required for antitumor activity in NRAS/ KRAS mutant tumors when compared to BRAF mutant tumors. A weekly dosing schedule can therefore be expected to achieve higher unit doses, which may allow achievement of higher MLN2480 concentrations, and therefore a higher degree of pathway inhibition for a window of time within the dosing interval, without compromising overall dose density. Once the MTD/ recommended phase 2 dose (RP2D) is established for the QW Dose Escalation phase, a QW Dose Expansion phase will test MLN2480 in 2 melanoma expansion cohorts.

Procedural information regarding the addition of the QW Dose Escalation and Dose Expansion phases has been added throughout the protocol. Other substantive changes include clarifying the melanoma cohort definitions, clarifying the dose modifications for toxicity, permitting intrapatient dose escalation for patients, and updating the SAE reporting contact information.

Other clarifications to procedures are captured in the following bullets.

Purposes for Amendment 6

The purposes of this amendment are to:

- Increase the number of study centers to account for newly added QW dose cohorts
- Add a QW dosing schedule to the study
- Permit patients on the 22-day treatment cycle to switch to the 28-day treatment cycle
- Add study procedures for a QW Dose Escalation phase
- Add procedures for a QW Dose Expansion phase
- Add alternative QW dosing schedules (BID and split over 2 days) to both the Escalation and Expansion phases, if necessary to increase systemic exposures
- Clarify tumor tissue sampling requirements to include QW cohorts
- Relocate the 22-Day Treatment Cycle SOE Tables to an appendix

- Update scientific background to reflect that some RAF kinase inhibitors are commercially available
- Add rationale for implementation of QW Dosing Schedule
- Modify the primary objectives of the study to include QW dose schedule assessment
- Update the number of patients in the study to reflect addition of QW Dose Escalation and Dose Expansion cohorts
- Modify inclusion criteria to reflect Q2D or QW dose schedule and clarify melanoma cohort definitions
- Clarify the inclusion criterion regarding previous chemotherapy, immunotherapy, and hormone therapy
- Allow intrapatient dose escalation for patients in the Dose Escalation phase in dose cohorts below the MTD/RP2D
- Clarify the dose modification guidelines
- Update SAE Reporting Contact Information from PPDI to Cognizant
- Correct typographical errors, punctuation, grammar, and formatting

14.10 Amendment 7 Summary of Changes

Rationale for Amendment 7

The primary purpose of this amendment is to add text detailing the management of cardiac events, based on an assessment of cardiac risk in patients treated with MLN2480 and on reports of cardiotoxicity associated with some BRAF inhibitors. To further evaluate this potential risk, ECHO and MUGA assessments have been added to the Schedules of Events.

This amendment redefines the eligibility criteria for Cohort 8 (QW Dose Expansion phase). The approximately 16-patient cohort will now be comprised of approximately 8 patients who are treatment naïve and approximately 8 patients who are relapsed and/or refractory to prior treatment with RAF inhibitors and/or MEK inhibitors.

This amendment also clarifies the number of pharmacokinetic (PK) samples needed from patients on the QW dose schedule. A total of 16 evaluable patients are required for the QW schedule, inclusive of patients treated at the established maximum tolerated dose (MTD) / recommended phase 2 dose (RP2D) in the dose escalation phase and the dose expansion phase.

Purposes for Amendment 7

The purposes of this amendment are to:

- Add collection of ECHO/MUGA assessments to the Schedules of Events
- Increase the number (range) of study centers in the US for the QW Dose Escalation phase
- Redefine the eligibility criteria for Cohort 4

- Redefine the number of subjects and eligibility criteria for Cohort 8
- Add a definition of the permitted LVEF, as measured by ECHO or MUGA, to the study inclusion criteria
- Clarify the number of patients on the QW dose schedule who need a postdose fresh biopsy
- Add recommendations for treatment should a patient experience a cardiac event during treatment with MLN2480
- Add ECHO and MUGA assessments to the study procedures
- Add thyroid function test to the list of blood chemistry evaluations
- Correct typographical errors, punctuation, grammar, and formatting

14.11 Amendment 8 Summary of Changes

Rationale for Amendment 8

The primary purpose of this amendment is to provide notification that enrollment into Cohort 8 is discontinued as of this amendment (Amendment 8).

Purposes for Amendment 8

The purposes of this amendment are to:

- Clarify the description of dosing cohorts by removing the term "melanoma" expansion cohorts and replacing with "dose" expansion cohorts since not all cohorts are melanoma cohorts (ie, Cohort 7).
- Clarify procedures for pretreatment adverse event recording and reporting of suspected unexpected serious adverse reactions (SUSARS) to regulatory authorities.
- Update section on monitoring of adverse events (AEs).
- Clarify language regarding the recording of AEs during Screening.
- Provide updated language that enrollment into Cohort 8 is discontinued as of this amendment (Amendment 8).
- Revise language on the collection of tumor tissue samples to indicate that pharmacokinetic and correlative biomarker analysis will be conducted.
- Clarify procedures for obtaining archived / fresh tumor biopsies for genotyping in the Q2D and QW Expansion cohorts at Screening.
- Revise timepoint from postdose to predose for collection of Day 22 plasma samples for biomarker assessment and circulating tumor DNA and retrieval of fresh tumor biopsy for QW 28-Day Treatment Cycle: Cycle 1 Schedule Treatment Cycle: Cycle 1 Schedule.
- Clarify the Day 1 time window (± 2 days) for timing of procedures for the Q2D 28-Day Treatment Cycle: Cycle 2 Schedule, the QW 28-Day Treatment Cycle: Cycle 2 Schedule, and the 22-Day Treatment Cycle: Cycle 2 Schedule.
- Clarify footnotes that apply to the requirement for obtaining paired tumor biopsies.
- Clarify footnote that describes the Q2D melanoma expansion cohorts during Q2D 28-

Day Treatment Cycle: Cycle 1 Schedule.

- Revise footnote to indicate that the timing of assessments during the Q2D 28-Day Treatment Cycle: Cycle 1 Schedule refers to pharmacokinetic assessments and not biomarker assessments.
- Revise language on once weekly (QW) dosing to indicate that melanoma or solid tumor patients may be enrolled in the QW Expansion cohorts.
- Revise inclusion criteria to include patients with solid tumors.
- Revise inclusion criteria to change the number of patients required to have paired biopsies from 16 to 8 patients.
- Remove inclusion criteria that indicate that patients in the melanoma expansion cohorts must have a fresh tumor biopsy at Screening. Language has been clarified throughout the protocol to indicate that archival tissue is acceptable where appropriate.
- Update contraception language from 3 months to 120 days (4 months).
- Update the time period allowed for archival of tissue or tumor biopsy samples from 12 months to 24 months.
- Correct the dose increase factor for the table on QW planned dose levels from 20% to 25%.
- Remove reference to the Pharmacy Manual in the section on study drug administration.
- Update the section on study drug administration to remove the 5 mg tablet, to include the 70 mg tablet and to provide additional details regarding the optimized formulation.
- Clarify the three MLN2480 dosage strengths to be used in the study.
- Remove the section on packaging and labeling as this section is contained in the revised section on study drug administration.
- Provide updated contact information for product complaints.
- Update contact information for the Global Clinical Lead.
- Correct typographical errors, punctuation, grammar, and formatting.

14.12 Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 9 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Changed the information for the signatories on the title page.

The primary change occurs on the Title Page:

Initial wording:	PPD
Amended or new wording:	PPD

Rationale for Change:

Information was changed to reflect changes in Takeda processes and personnel.

Change 2: Added a Schedule of Events with reduced assessments (12-week [84-day] treatment cycle) for patients in the study for 4 years or longer.

The primary change occurs in the new Schedule of Events for the 12-Week (84-Day) Treatment Cycle for Patients in the Study for 4 Years or Longer:

Description of change: A new schedule of events was added showing assessments for the 12-week (84-day) treatment cycle for patients who are in the study for 4 years or longer:

- Physical examination and body weight at Day 1 ±14 days
- Dermatological exam at Day 1 ±14 days
- Vital signs (temperature, blood pressure, pulse rate) at Day 1 ±14 days
- Laboratory tests (thyroid function, urinalysis, hematology, blood chemistry) at Day 1 ±14 days
- Disease assessment, including CT or MRI scan every 6 months ±14 days
- Creatine kinase every 6 months ±14 days
- 12-lead ECG every 6 months ±14 days
- SAE reporting: SAEs will be collected from signing of informed consent form through 30 days after the last dose of study drug
- MLN2480 Q2D administration: continuous dosing

Rationale for Change:

Many of the original assessments are no longer required for patients in the study for 4 years or longer and after the planned database lock for this study.

Change 3: Introduced TAK-580, the new product code for MLN2480.

The primary change occurs in Section 1.1 Scientific Background:

Added text: MLN2480**, currently known as TAK-580,** is a potent, small molecule pan-RAF kinase inhibitor being developed for the treatment of solid tumors, including locally advanced, metastatic, and/or unresectable melanoma.

Rationale for Change:

The new product code is being introduced in clinical documents when they are updated.

Change 4: Added that patients in the study for 4 years or longer will take MLN2480 every other day in 12-week (84-day) treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason.

The primary change occurs in Section 4.3 Duration of Study:

Added text:	During the Treatment period, patients will take MLN2480 orally Q2D in 22- or 28-day treatment cycles or QW in 28-day treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months**. Patients in the study for 4 years or longer will take MLN2480 Q2D in 12-week (84-day) treatment cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason.**

Rationale for Change:

The study duration for patients on 12-week treatment cycles was added for consistency with the text regarding patients on other dosing/treatment cycles.

Change 5: Added that when patients have been in the study for 4 years or longer, nonserious adverse events will no longer be reported.

The primary change occurs in Section 9.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Added text:	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**. When patients have been in the study for 4 years or longer, nonserious AEs will no longer be recorded.**

Rationale for Change:

Adequate nonserious AE data have been collected; therefore, only SAEs will be reported for these patients in accordance with the ICH-GCP and appropriate regulatory requirement(s).

Section 9.3 Monitoring of Adverse Events and Period of Observation also contains this change.

Change 6: Changed the name and telephone number of the call center for product complaints.

The primary change occurs in Section 10.11 Product Complaints:

Initial wording:	A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative. **For Product Complaints,** For more information call 1-866-835-2233 or email GlobalOncologyMedinfo@takeda.com
Amended or new wording:	A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact ~~MedComm Solutions~~ **the Medical Information Call Center (Dohmen Life Science Services [DLSS])** (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative. **For Product Complaints,** For more information call ~~1-866-835-2233~~ **1-844-ONC-TKDA (1-844-662-8532)** or email GlobalOncologyMedinfo@takeda.com

Rationale for Change:

The name and telephone number of the call center have changed.