Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer

NCT02719691

July, 25, 2018

CLINICAL STUDY PROTOCOL

COMIRB 15-1135
Takeda Protocol X31023

A phase Ib study of the combination of MLN0128 (Dual TORC1/2 Inhibitor) and MLN8237 (Aurora A inhibitor, alisertib) in patients with advanced solid tumors with an expansion cohort in metastatic triple-negative breast cancer (TNBC)

Indication: Advanced solid tumors, triple-negative breast cancer
Phase: Ib

Protocol History

Version 1	13 Oct 2015
Version 1.1	01 Dec 2015
Version 2	23 Mar 2017
Version 3	09 May 2018
Version 4	25 July 2018

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This is an investigator-initiated study. The principal investigator Jennifer R. Diamond, (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY
Study Title: A phase Ib study of the combination of MLN0128 (Dual TORC1/2 Inhibitor) and MLN8237 (Aurora A inhibitor, alisertib) in patients with advanced solid tumors with an expansion cohort in metastatic triple-negative breast cancer (TNBC)
Phase: Ib
Number of Patients: A maximum of 6 patients can be enrolled at each dose level. With 5 potential dose levels and an expansion cohort of 30 patients, including TNBC, the maximum number of patients that can be enrolled is 56 and the minimum number is 6.
Study Objectives Primary • To determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of the combination of MLN0128 and alisertib in adult patients with advanced solid tumors. Secondary • To determine the safety profile and tolerability of the combination of MLN0128 and alisertib in adult patients with advanced solid tumors. • To determine the pharmacokinetics of MLN0128 and alisertib in the combination. • To evaluate the pharmacodynamic effects of MLN0128 and alisertib in serial tumor biopsies and blood samples in patients with metastatic TNBC and other solid tumors enrolled in the expansion cohort at the MTD. • To estimate the objective response rate using RECIST 1.1 and time to progression in patients with advanced solid tumors treated with MLN0128 and alisertib. Tertiary/Exploratory • To explore biomarkers predictive of response to MLN0128 and alisertib including the investigation of mechanisms of acquired resistance to treatment in patients with metastatic TNBC and other solid tumors treated in the expansion cohort at the MTD. • To evaluate the pharmacodynamic effect of the combination of MLN0128 and alisertib on cellular metabolism using functional imaging with FDG-PET (5-fluoro-deoxy-glucose-PET) and diffusion weighted magnetic resonance imaging (DWI-MRI).
Overview of Study Design: This is a single institution, Phase Ib study designed to evaluate the safety and toxicity of the combination of MLN0128 and alisertib in patients with advanced solid tumors with an expansion cohort in patients with previously treated metastatic TNBC and other solid tumors. The dose escalation portion of the trial with be conducted using a standard 3 + 3 dose-escalation design in patients with advanced solid tumors refractory to standard therapies or where no standard therapy exists (see Figure 1 for dose escalation

schema and Table 1 for planned dose levels). Once the maximum tolerated dose (MTD) / recommended phase II dose (RP2D) is identified, the dose expansion portion will be conducted in patients with previously treated metastatic TNBC and other solid tumors. Exploratory correlative studies will be conducted in the expansion cohort including: evaluation of pharmacodynamics markers in serial tumor biopsies and blood samples, exploration of predictive biomarkers using fresh and archival tissue samples, and evaluation of cellular metabolism using functional imaging.

A total of 20 patients will be treated in the dose-expansion cohort at the MTD/RP2D (see Figure 2 for dose expansion cohort schema). All patients in the expansion cohort group 1 and 2, will be required to undergo a fresh tumor biopsy prior to initiating treatment, Cycle 1 Day 7, and Cycle 2 Day 7. In expansion cohort Group 1, single agent alisertib will be administered at the MTD on Days 1-7 and MLN0128 will be administered on Days 8-21. In Cycle 2 and beyond, dosing with both agents will begin on Day 1. In expansion cohort Group 2, MLN0128 will be administered at the MTD in Cycle 1 Days 1-28 and alisertib will be administered at the MTD on Days 8-15. An attempt will be made to obtain a repeat tumor biopsy at the time of progression in patients with an initial response to treatment in group 1 and 2. Objective tumor response using RECIST 1.1 will be evaluated every three cycles (approximately 9 weeks in the dose escalation cohort and 10 weeks in the dose expansion cohort Group 2).

An additional 10 patients with previously treated locally advanced or metastatic pancreatic cancer will be treated at the MTD/RP2D to further evaluate tolerability and explore efficacy in this population.

Study Population:

Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Dose Escalation Cohort: Patients must have a diagnosis of a histologically confirmed solid tumor that is incurable and refractory to standard therapy or for which no standard therapy exists.

3. Dose Expansion Cohort Group 1 and 2: Patients must have a diagnosis of histologically confirmed metastatic TNBC defined as negative for estrogen receptor, progesterone receptor and HER2. Patients must have received either adjuvant or first line chemotherapy for metastatic disease. Negative for Estrogen and Progesterone Receptor includes the following:
   - Local Pathology report classifies them as negative
   - Allred Score of 2 or below
   - <1% positive staining

   Subjects with solid tumor types other than TNBC may also be enrolled after

discussion with the Sponsor. These subjects must have a diagnosis of a histologically confimed solid tumor that is incurable and refractory to standard therapy or for which no standard therapy exists.

4. Pancreatic Cancer Cohort: Patients must have a diagnosis of locally advanced or metastatic pancreatic adenocarcinoma previously treated with or not a candidate for standard of care systemic therapy.
5. Dose Expansion Cohort Group 1 and 2: At least one tumor lesion amenable to repeat core needle biopsy or punch biopsy without unacceptable risk of a major procedural complication.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (See Appendix 1)
7. Three weeks or 5 half-lives (whichever is shorter) from previous systemic anticancer therapy; at least 4 weeks from major surgery and recovered; at least 2 weeks from palliative radiation and recovered. No more than 450 mg/m^2 cumulative dose of doxorubicin or equivalent anthracycline dose is allowed.
8. All acute treatment-related toxicities from prior therapy must have resolved to Grade ≤ 1 prior to study entry excluding alopecia.
9. For women:

    - Postmenopausal for at least 1 year before the screening visit, OR
    - Surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug OR agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence [e.g, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception

    For men, even if surgically sterilized (ie, status post-vasectomy), they must:

    - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence [e.g, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception
    - Agree not to donate sperm during the course of this study or 120 days after receiving their last dose of study drug
10. Screening clinical laboratory values as specified below:

a) Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; platelet count ≥ 100 x 10^9/L; hemoglobin ≥ 9 g/dL. Values must be obtained without the need for myeloid growth factor support, platelet or PRBC transfusion support within 14 days.

b) Hepatic: total bilirubin ≤ 1.5 x upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases are present);

c) Renal: Creatinine ≤ 1.5 X ULN or creatinine clearance ≥ 50 mL/min based either on Cockroft-Gault estimate or based on urine collection (12 or 24 hour)(Appendix 2);

d) Metabolic: Glycosylated hemoglobin (HbA1c)<7.0%, fasting serum glucose (≤ 130 mg/dL) and fasting triglycerides ≤ 300 mg/dL;

e) For patients undergoing serial tumor biopsies, INR and activated partial thromboplastin time (PTT) must be within 1.5 X the upper limit of normal.

11. Left ventricular ejection fraction (LVEF) ≥ LLN of the institutional standard of normal as measured by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) within 4 weeks prior to first study drug administration.

12. Ability to swallow oral medications.

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

14. Patients who have a history of brain metastasis are eligible for the study provided that all the following criteria are met:

    a) Brain metastases which have been treated

    b) No evidence of disease progression for ≥ 4 weeks or hemorrhage after treatment

c) Off-treatment with dexamethasone for 2 weeks before administration of the first dose of MLN0128

d) No ongoing requirement for dexamathasone or anti-epileptic drugs

Exclusion Criteria

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

1. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study.
2. Known human immunodeficiency virus infection.
3. Radiation therapy to more than 25% of the bone marrow. Whole pelvic radiation is considered to be over 25%.
4. Known history of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness, such as severe chronic obstructive pulmonary disease; requirement for supplemental oxygen.
5. Systemic infection requiring IV antibiotic therapy within 14 days preceding the first dose of study drug, or other severe infection.
6. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
7. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
8. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
9. Breast feeding or pregnant.
10. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128. In addition, patients with enteric stomata are also excluded.

11. Treatment with any investigational products within 3 weeks before the first dose of study drug.

12. History of any of the following within the last 6 months before administration of the first dose of the drug:

    a) Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures

    b) Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures

    c) Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia)

    d) Placement of a pacemaker for control of rhythm

    e) New York Heart Association (NYHA) Class III or IV heart failure (See Appendix 3)

    f) Pulmonary embolism

13. Significant active cardiovascular or pulmonary disease including:

    a) Uncontrolled hypertension (i.e., systolic blood pressure >180 mm Hg, diastolic blood pressure > 95 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed.

    b) Pulmonary hypertension

    c) Uncontrolled asthma or O_2 saturation < 90% by arterial blood gas analysis or pulse oximetry on room air

    d) Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement

    e) Medically significant (symptomatic) bradycardia

    f) History of arrhythmia requiring an implantable cardiac defibrillator

g) Baseline prolongation of the rate-corrected QT interval (QTc) (e.g., repeated demonstration of QTc interval > 480 milliseconds, or history of congenital long QT syndrome, or torsades de pointes)

14. Treatment with strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, CYP2C19 or CYP2C19 within 1 week preceding the first dose of study drug.

15. Patients receiving systemic corticosteroids (either IV or oral steroids, excluding inhalers or low-dose hormone replacement therapy) within 1 week before administration of the first dose of study drug.

16. Daily or chronic use of a proton pump inhibitor (PPI) and/or having taken a PPI within 7 days before receiving the first dose of study drug.

17. For patients undergoing serial tumor biopsies, known bleeding diathesis or history of abnormal bleeding or require anti-coagulation therapy which cannot be interrupted for biopsy.

Duration of Study: Patients will continue to receive treatment with MLN0128 and alisertib until they experience disease progression or have an unacceptable drug-related toxicity. There is no maximum duration of treatment. The study will be terminated 6 months after the last patient completes the End-of-Treatment (EOT) study visit.

STUDY OVERVIEW DIAGRAM

Figure 1. Dose Escalation Study Schema

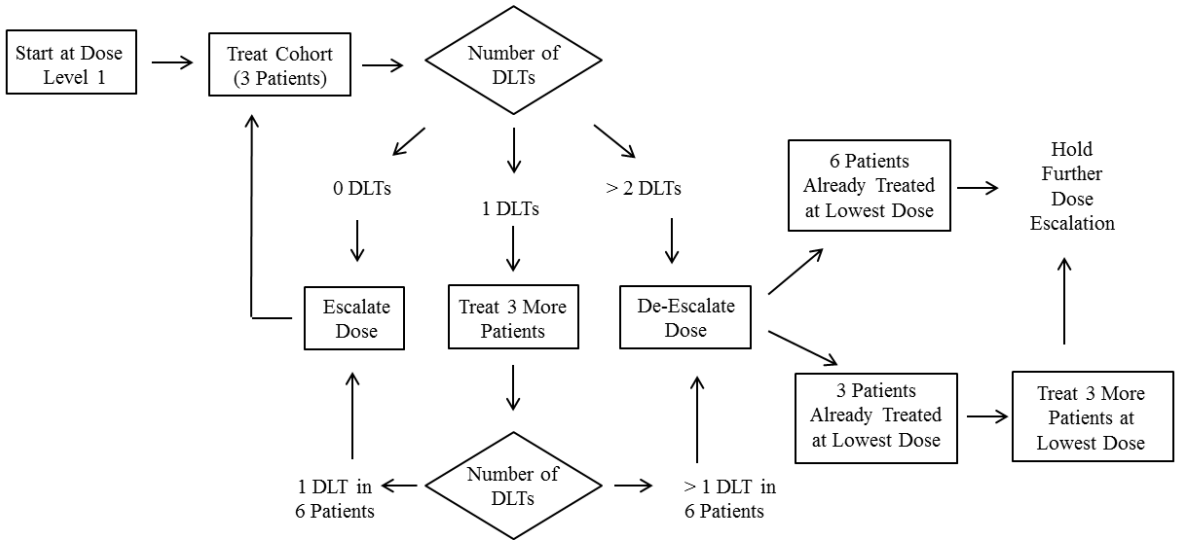
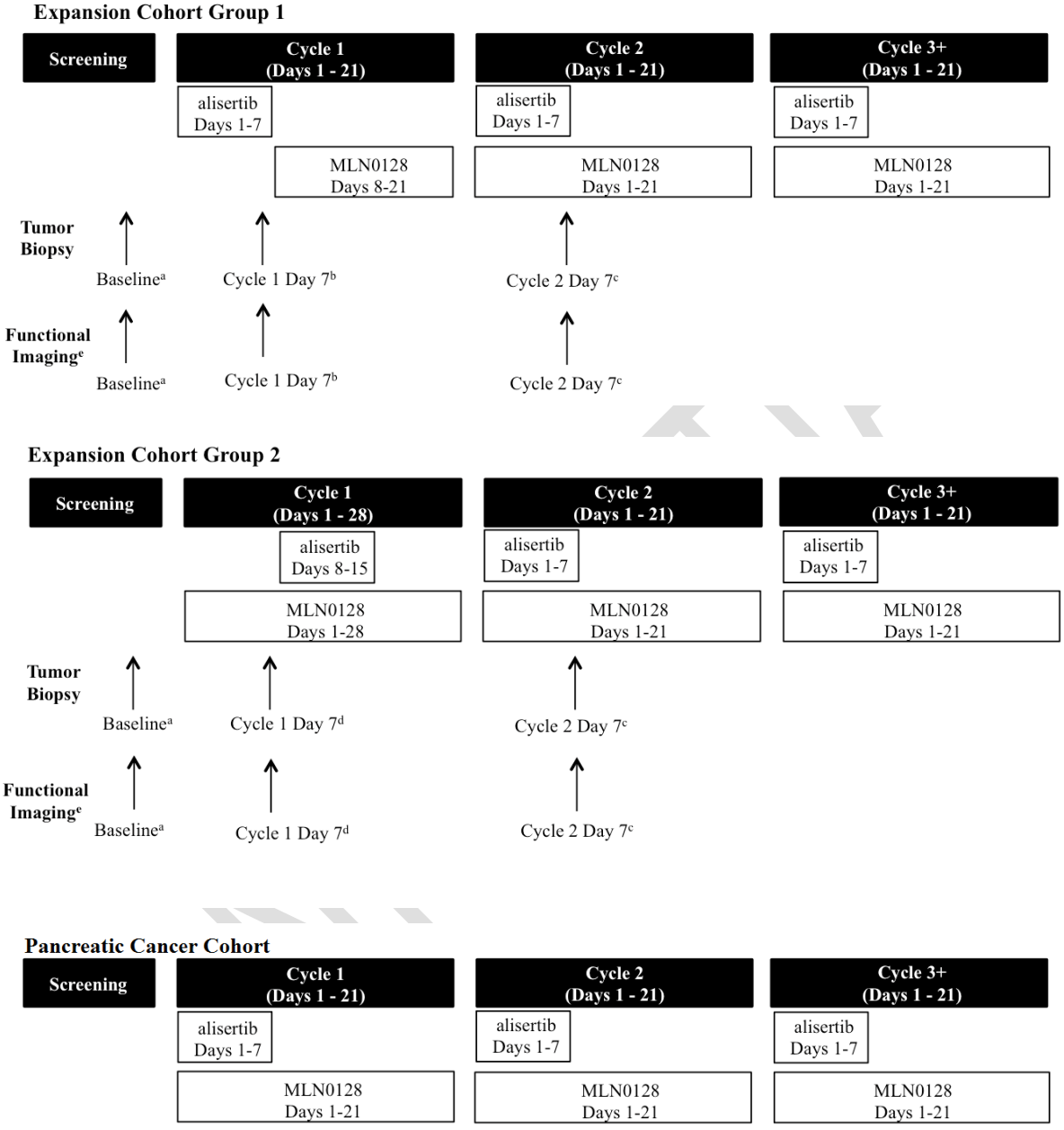


Figure 2. Dose Expansion Cohort Schema



a. Up to 28 days prior to initiation of treatment.
b. Up to 2 days prior to initiating MLN0128 dosing on Cycle 1 Day 7. Biopsy should be timed to occur within 5 hours after alisertib dosing, if possible.
c. Up to 2 days prior to Cycle 2 Day 7. Biopsy should be timed to occur within 5 hours after alisertib and MLN0128 dosing, if possible.
d. Up to 2 days prior to initiating alisertib dosing on Cycle 1 Day 8. Biopsy should be timed to occur within 5 hours after MLN0128 dosing, if possible.
e. DWI-MRI will be performed at Baseline, Cycle 1 Day 7 and Cycle 2 Day 7 in Group 1 and Group 2. For patients who undergo baseline FDG-PET/CT for evaluation of their disease, an additional FDG-PET may be performed for exploratory correlatives only at Cycle 2 Day 7. This scan will not be used to determine response to treatment. Functional imaging should be performed before the biopsy if the specific tumor biopsied is being followed on imaging. See Study Procedure Manual for additional details.

SCHEDULE OF EVENTS – Dose Escalation

		Cycle 1				Cycles 2-3			Cycle 4+	
Assessments[1]	Screening Day -28 to Day -1	C1 Day -7 to -3	C1D1	C1D7	C1D15	C2D1	C2D8	C2D15	D1	Termination
Inclusion/Exclusion	X	X								
Informed Consent and HIPAA Authorization	X									
Demographics, Medical/Cancer History including ER, PR and HER2 status (Breast Cancer Patients Only), tumor grade, stage, and prior therapy/dates/response	X									
ECHO/MUGA	X									
Physical Exam	X		X	X	X	X	X	X	X	X
Vitals	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X[2]	X	X	X	X	X	X	X	X
Hematology/Chemistry[3]	X	X[2]	X	X	X	X	X	X	X	X
Coagulation (PT/INR, aPTT)(Expansion Only)[4]	X			X			X[5]			
HbA1c	X								C3D1[6]	
Fasting serum glucose	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[7]	X					X			X	X
Urinalysis	X	X	X			X			X	X
Pregnancy Test[8]	X	X[2]				X			X	
In home daily fasting glucose monitoring[9]		X	X	X	X	X	X	X	X	X
Retained plasma and serum samples for Pharmacodynamics and Pharmacogenomics		X	X	X		X				
Plasma Sample Pharmacokinetics[10]		X	X	X		X	X		X	
MLN0128 Admin (oral daily Day 1-21, start Day 2 Cycle 1 only, single lead-in dose on Cycle 1 Day -7 to -3)[11]		X		X	X	X	X	X	X	
Alisertib Admin (oral BID Day 1-7, single dose on Cycle 1 Day 1 only)[11]			X	X		X			X	
DWI-MRI (Expansion Only)[12,]	X			X			X			
FDG-PET (Expansion Only)[13]	X						X			
Tumor Biopsy (Expansion Only)	X			X			X[5]			

Radiographic Tumor Response Evaluation [14]	X								X Cycle 4 Day 1	
ECG (locally read)[15]	X	X				X				X
Con Med Assessment	X	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X	X

[1] With the exception of EKGs, assessments may be done within 24-48 hours of MLN0128 or alisertib administration

[2] Repeated only if more than 96 hours since screening assessments. Assessments must continue to be acceptable if repeated at baseline.

[3] CBC with differential, electrolyte panel, LFTs and kidney function tests, total protein, calcium, phosphate, magnesium

[4] Coagulation tests must be within 1.5 X ULN and platelets > 75,000 within 24 hours of biopsy

[5] Tumor biopsy should be performed C2 Day 6-7 in the Expansion Cohort. Functional imaging should be performed before the biopsy if specific tumor biopsied is being followed on imaging. See Study Procedure Manual for additional details.

[6] Should be repeated every 3 cycles for patients continuing on treatment.

[7] Total cholesterol, HDL, LDL and triglycerides

[8] Women of child bearing potential only

[9] Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight of for a minimum of 8 hours before the assessment) for each of these measurements. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.

[10] Blood samples for pharmacokinetic analysis will be drawn and processed Cycle 1 Day -7 to -3, Cycle 1 Day 1, and Cycle 1 Day 7. Samples will be obtained for MLN0128 PK on Cycle 1 Day -7 to -3 pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours. Samples will be obtained for alisertib PK on Cycle 1 Day 1 pre-dose and at 1, 2, 4, 6, 8, and 24 hours. Samples will be obtained for MLN0128 and alisertib PK on Cycle 1 Day 7 pre-dose and at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours. Samples will also be obtained pre-dose on Day 1 of Cycles 2+ and on the days of on treatment biopsies. There is a 5 minute window for the 0.25, 0.5 and 1.0 hour timepoints, a 30 minute window for the 2 - 6 hour timepoints and a 1 hour window for the 8 hour and 24 hour timepoints. Add additional PK sample will be obtained on the day of the on treatment tumor biopsies.

[11] For Expansion Cohort, see Figure 2 Dose Expansion Cohort Schema for dosing instructions.

[12] DWI-MRI will be performed at baseline, Cycle 1 Day 7 and Cycle 2 Day 7 in Expansion Cohort Group 1 and Group 2. See Figure 2 Dose Expansion Cohort Schema for more details. Functional imaging should be performed before the biopsy if specific tumor biopsied is being followed on imaging. See Study Procedure Manual for additional details.

[13] For patients who undergo baseline FDG-PET/CT for evaluation of their disease, an additional optional FDG-PET/CT may be performed for exploratory correlatives only at Cycle 2 Day 7. This scan will not be used to determine response to treatment. Functional imaging should be performed before the biopsy if specific tumor biopsied is being followed on imaging. See Study Procedure Manual for additional details.

[14] CT of the chest and abdomen is recommended in all patients; additional scans should be obtained depending on where baseline disease was known. MRI brain should be considered if clinical symptoms concerning for brain mets and is required in patients with previously treated brain mets. Scans must be performed within 28 days of starting study treatment. Imaging at Cycle 4 Day 1 and beyond may be performed within 7 days of Day 1. Imaging should be repeated every 3 cycles beyond Cycle 4.

[15] Single, 12-lead ECGs will be collected predose and 2 hours (± 30 min) postdose on Cycle 1, Day -7 to -3 and Cycle 2 Day 1. Further ECGs should be performed at the investigator's discretion if there are cardiac concerns or the patient experiences QTc prolongation in the scheduled ECGs.

SCHEDULE OF EVENTS – Expansion Group 1 and 2

		Cycle1			Cycles 2-3			Cycle 4+	
Assessments[1]	Screening Day -28 to Day -1	C1D1	C1D7	C1D15	C2D1	C2D8	C2D15	D1	Termination
Inclusion/Exclusion	X								
Informed Consent and HIPAA Authorization	X								
Demographics, Medical/Cancer History including ER, PR and HER2 status (Breast Cancer Patients Only), tumor grade, stage, and prior therapy/dates/response	X								
ECHO/MUGA	X								
Physical Exam	X	X	X	X	X	X	X	X	X
Vitals	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X[2]	X	X	X	X	X	X	X
Hematology/Chemistry[3]	X	X[2]	X	X	X	X	X	X	X
Coagulation (PT/INR, aPTT)(Expansion Only)[4]	X		X			X[5]			
HbA1c	X							C3D1[6]	
Fasting serum glucose	X	X	X	X	X	X	X	X	X
Fasting lipid profile[7]	X				X			X	X
Urinalysis	X	X			X			X	X
Pregnancy Test[8]	X				X			X	
In home daily fasting glucose monitoring[9]		X	X	X	X	X	X	X	X
Retained plasma and serum samples for Pharmacodynamics and Pharmacogenomics		X			X			X	X
Plasma Sample Pharmacokinetics[10]		X	X		X	X		X	
MLN0128 Admin (oral daily Day 1-21, start Day 2 Cycle 1 only, single lead-in dose on Cycle 1 Day -7 to -3)[11]			X	X	X	X	X	X	
Alisertib Admin (oral BID Day 1-7, single dose on Cycle 1 Day 1 only)[11]		X	X		X			X	
DWI-MRI (Expansion Only)[12, 16]	X		X			X			
FDG-PET (Expansion Only)[13]	X					X			
Tumor Biopsy (Expansion Only)[16]	X		X			X[5]			

Radiographic Tumor Response Evaluation [14]	X							X Cycle 4 Day 1	
ECG (locally read)[15]	X				X				X
Con Med Assessment	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X

[1] With the exception of EKGs, assessments may be done within 24-48 hours of MLN0128 or alisertib administration

[2] Repeated only if more than 96 hours since screening assessments. Assessments must continue to be acceptable if repeated at baseline.

[3] CBC with differential, electrolyte panel, LFTs and kidney function tests, total protein, calcium, phosphate, magnesium

[4] Coagulation tests must be within 1.5 X ULN and platelets > 75,000 within 24 hours of biopsy

[5] Tumor biopsy should be performed C2 Day 6-7 in the Expansion Cohort. Functional imaging should be performed before the biopsy if specific tumor biopsied is being followed on imaging. See Study Procedure Manual for additional details.

[6] Should be repeated every 3 cycles for patients continuing on treatment.

[7] Total cholesterol, HDL, LDL and triglycerides

[8] Women of child bearing potential only

[9] Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight of for a minimum of 8 hours before the assessment) for each of these measurements. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.

[10] Blood samples for pharmacokinetic analysis will be drawn and processed Cycle 1 Day 1, Cycle 1 Day 7. Cycle 2 Day 1, Cycle 2 Day 8 and Cycles 3+ Day 1 predose.

[11] For Expansion Cohort, see Figure 2 Dose Expansion Cohort Schema for dosing instructions.

[12] DWI-MRI will be performed at baseline, Cycle 1 Day 7 and Cycle 2 Day 7 in Expansion Cohort Group 1 and Group 2. See Figure 2 Dose Expansion Cohort Schema for more details. Functional imaging should be performed before the biopsy if specific tumor biopsied is being followed on imaging. See Study Procedure Manual for additional details.

[13] For patients who undergo baseline FDG-PET/CT for evaluation of their disease, an additional optional FDG-PET/CT may be performed for exploratory correlatives only at Cycle 2 Day 7. This scan will not be used to determine response to treatment. Functional imaging should be performed before the biopsy if specific tumor biopsied is being followed on imaging. See Study Procedure Manual for additional details.

[14] CT of the chest and abdomen is recommended in all patients; additional scans should be obtained depending on where baseline disease was known. MRI brain should be considered if clinical symptoms concerning for brain mets and is required in patients with previously treated brain mets. Scans must be performed within 28 days of starting study treatment. Imaging at Cycle 4 Day 1 and beyond may be performed within 7 days of Day 1. Imaging should be repeated every 3 cycles beyond Cycle 4.

[15] Single, 12-lead ECGs will be collected predose and 2 hours (± 30 min) postdose on Cycle 1 Day 1 and Cycle 2 Day 1. Further ECGs should be performed at the investigator's discretion if there are cardiac concerns or the patient experiences QTc prolongation in the scheduled ECGs.

SCHEDULE OF EVENTS – Pancreatic Cancer Cohort

		Cycle 1			Cycles 2-3			Cycle 4+	
Assessments[1]	Screening Day -28 to Day -1	C1D1	C1D8	C1D15	C2D1	C2D8	C2D15	D1	Termination
Inclusion/Exclusion	X								
Informed Consent and HIPAA Authorization	X								
Demographics, Medical/Cancer History including ER, PR and HER2 status (Breast Cancer Patients Only), tumor grade, stage, and prior therapy/dates/response	X								
ECHO/MUGA	X								
Physical Exam	X	X	X	X	X	X	X	X	X
Vitals	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X[2]	X	X	X	X	X	X	X
Hematology/Chemistry[3]	X	X[2]	X	X	X	X	X	X	X
HbA1c	X							C3D1[4]	
Fasting serum glucose	X	X	X	X	X	X	X	X	X
Fasting lipid profile[5]	X				X			X	X
Urinalysis	X	X			X			X	X
Pregnancy Test[6]	X				X			X	
In home daily fasting glucose monitoring[7]		X	X	X	X	X	X	X	X
Retained plasma and serum samples for Pharmacodynamics and Pharmacogenomics		X			X				X
Plasma Sample Pharmacokinetics[8]		X			X			X	
MLN0128 Admin [9]		X			X			X	
Alisertib Admin [9]		X			X			X	
Radiographic Tumor Response Evaluation [10]	X							X Cycle 4 Day 1	
ECG (locally read)[11]	X								
Con Med Assessment	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X

[1] With the exception of EKGs, assessments may be done within 24-48 hours of MLN0128 or alisertib administration
[2] Repeated only if more than 96 hours since screening assessments. Assessments must continue to be acceptable if repeated at baseline.
[3] CBC with differential, electrolyte panel, LFTs and kidney function tests, total protein, calcium, phosphate, magnesium
[4] Should be repeated every 3 cycles for patients continuing on treatment.
[5] Total cholesterol, HDL, LDL and triglycerides
[6] Women of child bearing potential only
[7] Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight of for a minimum of 8 hours before the assessment) for each of these measurements. In-home glucose monitoring is not

required on days when fasting glucose is measured in the clinic.

[8] Blood samples for pharmacokinetic analysis will be drawn and processed Cycle 1 Day 1, Cycle 2 Day 1 and Cycles 3+ Day 1 predose.

[9] For Expansion Cohort, see Figure 2 Dose Expansion Cohort Schema for dosing instructions.

[10] CT of the chest and abdomen is recommended in all patients; additional scans should be obtained depending on where baseline disease was known. MRI brain should be considered if clinical symptoms concerning for brain mets and is required in patients with previously treated brain mets. Scans must be performed within 28 days of starting study treatment. Imaging at Cycle 4 Day 1 and beyond may be performed within 7 days of Day 1. Imaging should be repeated every 3 cycles beyond Cycle 4.

[11] Single, 12-lead ECGs will be collected at screening. Further ECGs should be performed at the investigator's discretion if there are cardiac concerns or the patient experiences QTc prolongation in the scheduled ECGs.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT3	5-hydroxytryptamine 3
AE	adverse event
AKI	aurora kinase inhibitor
AKT	protein kinase B
ALP/ SGPT	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
AST/ SGOT	aspartate aminotransferase
ATP	adenosine 5'triphosphate
AUC	area under curve
AurA	Aurora kinase A
BCRP	breast cancer resistance protein
BID	bis in die; twice a day
BRCA1	breast cancer susceptibility gene
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CV	cardiovascular; coefficient of variation
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
DWI-MRI	Diffusion-weighted MRI
EC	ethics committee
ECG	electrocardiogram; electrocardiography
ECT	enteric coated tablet
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ER	estrogen receptor
4EBP1	eukaryotic translation Initiation Factor 4E-binding Protein 1
FDG-PET	5-fluoro-deoxy-glucose-PET
FSG	fasting serum glucose
Hb	hemoglobin
HbA1c	glycosylated hemoglobin

Abbreviation	Term
HEENT	head, eyes, ears, nose and throat
hERG	human ether-à-go-go related gene
IRB	Intitutional review board
GI	gastrointestinal
GLP	good laboratory practice
H2	histamine-2
HER2	human epidermal growth factor 2
HDL	high-density lipoprotein cholesterol
HDPE	high-density polyetylene
ICF	informed consent form
IC_{50}	concentration producing 50% inhibition
INR	international normalized ratio
IV	intravenous(ly)
IVF	intravenous fluids
KD	knock-down
LDL	low-density lipoprotein cholesterol
LFT	liver function test(s)
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MM	multiple myeloma
MOA	mechanism of action
MTD	maximum tolerated dose
mTOR	mechanistic target of rapamycin
mTORC[1] or [2]	target of rapamycin complex [1 or 2]
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non- Hodgkin Lymphoma
NYHA	New York Heart Association
OCT	organic cation transporter [1 or 2]
PBL	peripheral blood lymphocytes
PK	pharmacokinetic(s)
PD	pharmacodynamic(s)
PDX	patient-derived tumor xenograft
PGx	pharmacogenomic(s)
PO	*per os*; by mouth (orally)
PPI	Protein pump inhibitor

Abbreviation	Term
PR	Progesterone receptor
PRBC	Packed red blood cells
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	once daily
QD×3days per week	once daily for 3 consecutive days followed by a 4-day dosing holiday every week
QD×5days per week	once daily for 5 consecutive days followed by a 2-day dosing holiday every week
QT	interval on ECG between the start of the Q wave and end of the T wave
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	once weekly
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
SA-β-gal	senescence associated-β-galactosidase
SAE	serious adverse event
SD	standard deviation
TGI	tumor growth inhibition
tmax	time to reach Cmax
TIA	Transient ischemic attack
TNBC	triple-negative breast cancer
TPN	total parental nutrition
ULN	upper limit of normal
WM	Waldenström macroglobulinemia

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Metastatic Triple-Negative Breast Cancer

Breast cancer is the most prevalent malignancy in women worldwide and accounts for more than 400,000 cancer deaths annually (1). Triple-negative breast cancer (TNBC) is defined as breast cancer which is negative for the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC accounts for 10-15% of all newly diagnosed breast cancer (2,3), although there is a higher incidence in breast cancer susceptibility gene (BRCA1) mutation carriers (4) in African-American women (5). The molecular profiling of breast cancers has revealed that a basal-like gene expression signature most commonly characterizes TNBC; however, the overlap is not complete (6,7). Patients with TNBC are more likely to develop distant metastasis and have an increased risk of death from breast cancer compared to other breast cancer subtypes (2,8).

Systemic chemotherapy is the mainstay of treatment for advanced or metastatic TNBC (9). The principle goal of chemotherapy in metastatic breast cancer is the palliation of symptoms related to sites of disease; however, prolongation of survival is also a goal where feasible. Combination chemotherapy generally has higher response rates compared to the sequential administration of single agents. Combination chemotherapy, however, does not always confer a survival benefit and can produce significantly more toxicity (10). First line chemotherapy for TNBC generally involves an anthracycline or taxane-based regimen. A number of other chemotherapeutic agents have some degree of activity (11) and there are currently no targeted agents FDA-approved for the treatment of TNBC. Patients with metastatic TNBC have a median overall survival of around 13 months and a median duration of first line therapy of just 12 weeks (12).

1.1.2 MLN0128

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

MLN0128 selectively and potently inhibits mTOR kinase (IC_{50} = 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation. The mTOR is a kinase that regulates cell growth, translational control, angiogenesis, and cell survival by integrating nutrient and hormonal signals. mTOR kinase plays a key role in several pathways that are requently dysregulated in human cancer (13). mTORC1 is best known as a key regulator of protein translation through phosphorylation of 4EBP1 (the eukaryotic translation Initiation Factor 4E-binding Protein 1) and ribosomal protein S6 (known as S6) kinase. mTORC2 is best known for its ability to fully activate protein kinase B (AKT) by phosphorylation on the S473 site, which regulates proliferation and survival pathways (14).

The mTORC is an important therapeutic target that is a key intracellular point of convergence for a number of cellular signaling pathways. Inhibiting mTOR may inhibit

abnormal cell proliferation,tumor angiogenesis, and abnormal cellular metabolism, thus providing the rationale for mTOR inhibitors as potential agents in the treatment of a number of indications including solid tumor and hematological malignancies, as either monotherapy or in combination with other chemotherapeutic agents. Like rapamycin, several newly approved rapalogs (temsirolimus and everolimus) are specific and allosteric inhibitors of mTORC1, and only partially inhibit mTORC1 signaling pathways. They do not directly inhibit mTORC2, which has shown to be an emerging target in cancer research. MLN0128 was developed to address the incomplete inhibition of the mTOR pathway by rapalogs by targeting both mTORC1 and mTORC2.

MLN0128 is being developed for both oncology and non-oncology indications. In oncology, MLN0128 is being investigated as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or antihormonal agents. Non-oncology indications being investigated include fibrotic and inflammatory diseases.

2. NONCLINICAL SUMMARY

2.1 Pharmacology

MLN0128 selectively and potently inhibits mTOR kinase (the concentration inhibiting 50% of enzyme activity [IC_{50}] is 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation.

MLN0128 inhibited phosphorylation of downstream modulators of mTORC1and mTORC2 in human U87 glioblastoma tumor xenograft models in mice and showed strong tumor growth inhibition (TGI) at tolerable oral (PO) doses in all 8 xenograft models tested (see IB Ed8 for details).

2.2 Safety Pharmacology

MLN0128 has a low potential to affect the human ether-à-go-go related gene (hERG) potassium ion channel and did not affect cardiovascular (CV) parameters in vivo in telemeterized monkeys.

2.3 Drug Metabolism and Pharmacokinetics

MLN0128 was rapidly absorbed after PO administration to mice, rats, dogs, and monkeys, with high oral bioavailability. [^{14}C]MLN0128 was rapidly and widely distributed throughout the body in Long-Evans rats; radioactivity was eliminated from most tissues at 48 hours postdose. MLN0128 displayed dose-proportional plasma exposures, a moderate propensity to cross the blood-brain barrier, and was modestly bound (70.5%) to human plasma proteins. MLN0128 distributed mainly to the plasma of human blood. There was no obvious concentration-dependent red blood cell (RBC) distribution of MLN0128 in human

blood.

MLN0128 did not inhibit P-glycoprotein, but did inhibit breast cancer-resistance protein (BCRP), organic cation transporter (OCT)1 and OCT2.

M1, the single metabolite (monohydroxylation product) observed in human microsomal incubations, was also observed in rats and monkeys. The main isozymes responsible for phase 1 metabolism appear to be cytochrome P450 (CYP) 2C9, 2C19, and 3A4. MLN0128 did not induce CYP1A2, 2B6, and 3A4 activity and expression at concentrations up to 10 μM. MLN0128 displayed low potential for inhibition and is not a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

Oral administration of MLN0128 in humans has a low potential for metabolic and transporter-based drug-drug interactions (DDIs), especially given clinical exposures observed to date after administration of the highest anticipated therapeutic dose to be used in the clinic in oncology indications (total maximum plasma concentration [C_{max}] of 0.48 μM [free C_{max} of 0.14 μM] at 30 mg once weekly [QW]).

2.4 Toxicology

The toxicologic profiles obtained in the Good Laboratory Practice (GLP)-compliant and non-GLP-compliant studies in rats and monkeys were generally consistent with pharmacologic inhibition of mTORC1/2 activity. Observed toxicities were mostly consistent between sexes. MLN0128 repeat-dose GLP studies include completed 28-day and preliminary 3-month toxicology studies in rat and monkeys, and embryo-fetal studies in rats and rabbits.

The primary dose-limiting toxicities (DLTs) of MLN0128 in rats and monkeys were secondary to an exaggerated pharmacologic response and consisted of body weight loss and associated clinical observations that included hunched posture, dehydration, gastrointestinal (GI) distress and decreased activity, appetite, and body temperature. In addition to the previously mentioned effects, a single monkey in the 3-month toxicology study demonstrated a DLT of skin toxicity characterized as progressive acanthosis. The highest exposures tolerated in the preliminary 3-month rat and monkey toxicology studies were 1233 and 194 ng·hr/mL, respectively.

Adverse effects in rats included body weight loss, decreased activity, increased glucose and insulin levels, alterations in white blood cells, bone marrow and lymphoid depletion, thymic necrosis, oligospermia, testes degeneration/atrophy, nonglandular stomach epithelial degeneration/ulceration/hyperplasia, pancreatic islet degeneration and fibrosis, lens fiber degeneration with cataract correlate, adrenal cortex hypertrophy, pituitary atrophy secondary to body weight loss, liver hepatocellular vacuolation, retinal dysplasia with or without optic nerve atrophy, and alveolar histiocytosis. The alveolar histiocytosis was only present in the 28-day rat study and was absent in the 3-month rat study. Both retinal dysplasia and alveolar histiocytosis are thought to be potential background findings. The pancreatic islet degeneration and fibrosis, as well as the other findings of lens fiber degeneration, pituitary atrophy, and liver vacuolation, were consistent with the mechanism of action (MOA) and

effects observed with other rapalogs. The microscopic findings observed in the testes, epididymides, and eyes in the 28-day and/or 3-month rat studies were not resolved after a 14-day recovery period, while partial to complete resolution was seen in the pancreas, adrenal gland, pituitary, liver, lungs, thymus, nonglandular stomach, and bone marrow.

The adverse effects in monkeys included hunched posture, dehydration, GI distress, and decreased activity, appetite, and body weight; increased glucose and insulin; lymphoid and bone marrow depletion; adrenal hypertrophy/hyperplasia; pancreatic and salivary gland acinar cell secretory depletion; neutrophilic inflammation of GI tract with occasional erosion and ulceration, skin effects including ulceration, epidermal hyperplasia, acanthosis and hyperkeratosis; and adipose tissue depletion. Additionally, there were sporadic inflammatory findings among some animals that were of uncertain association to the test article. The findings in the pancreas, adrenal glands, and salivary glands may have been related to a stress response or reduced food consumption. The findings observed in repeat-dose monkey studies were generally reversible after a 14-day recovery period.

The findings in rat and monkey repeat-dose toxicology studies with MLN0128, including bone marrow and lymphoid depletion; GI, liver, pancreas, and skin effects; and effects on glucose and insulin levels, can be monitored in clinical trials. The toxicities seen in the repeat-dose toxicology studies, such as GI effects and glucose and insulin increases, are consistent with the treatment-emergent adverse events (TEAEs), including mucositis and hyperglycemia, observed to date in patients receiving MLN0128.

Rat and rabbit range-finding embryo-fetal studies demonstrated teratogenic, fetotoxic, and abortive effects with MLN0128. Embryo-fetal lethality and/or teratogenic effects have been reported with the mTORC1 inhibitors rapamycin and the rapalogs.

MLN0128 was negative for genotoxicity in an in vitro bacterial mutagenesis (Ames) assay, an in vivo rat micronucleus assay, and an in vivo rat comet assay. An in vitro chromosomal aberration assay with MLN0128 in human peripheral blood lymphocytes (PBLs) was positive for chromosomal aberrations in the presence and absence of metabolic activation. However, the weight of evidence from the combined results of a negative mutagenicity assay and negative genotoxicity assessments in 2 in vivo assays in 3 tissues (bone marrow, liver, and duodenum) demonstrate that MLN0128 does not present a genotoxic risk. MLN0128 was negative for phototoxicity in the 3T3 fibroblast assay.

3. SUMMARY OF EFFECTS IN HUMANS

MLN0128 is in clinical development as a single agent in 3 phase 1 studies including study INK128-01 in patients with advanced solid malignancies, study INK128-002 in patients with multiple myeloma [MM], non-Hodgkin lymphoma [NHL] and Waldenström macroglobulinemia [WM]) and study C31002 to measure the effect of MLN0128 on QTc interval in patients with advanced solid malignancies. It is also being investigated in combination with paclitaxel (with or without trastuzumab) in patients with advanced solid tumors (Ph1 study INK128-003), and in combination with exemestane or fulvestrant in

women with ER+/HER2– (estrogen receptor-positive /human epidermal growth factor receptor 2 protein-negative) advanced or metastatic breast cancer (Ph1b/2 study C31001)

MLN0128 dosing regimens tested thus far include QD, QW, QD×3days per week (once daily for 3 consecutive days followed by a 4-day dosing holiday every week), and QD×5days per week (once daily for 5 consecutive days followed by a 2-day dosing holiday every week).

Please note that the data described in this section (sections 3.1 and 3.2) was obtained with the original unmilled MLN0128 active pharmaceutical ingredient (API); current manufacturing process produces milled MLN0128 API (see section 4).

3.1 Pharmacokinetics

Overall, pharmacokinetic (PK) data from Studies INK128-001, INK128-002, and INK128-003 indicate that MLN0128 exhibits fast oral absorption (time to reach C_{max} [t_{max}], generally between 1-4 hours after dosing); has dose-linear PK, with a mean plasma half-life of approximately 8 hours; and does not accumulate meaningfully in plasma when dosed as frequently as once daily (QD) and under any of 4 tested dosing regimens. The PK of MLN0128 was generally consistent, with no appreciable differences across the clinical studies that measured PK. Neither paclitaxel nor MLN0128 appeared to alter the PK of the other agent when co-administered.

3.2 Safety

As of the clinical data cutoff (09 December 2014), a total of 335 patients had received ≥ 1 dose of study drug across studies. A total of 18 deaths that occurred within 30 days of the last study drug dose had been reported to the clinical database as of the data cutoff; of these events, 1 (cardiac arrest; Study INK128-001) was considered related to MLN0128 (see section 5.3.1.1 of the IB Ed 8)

At least 1 treatment-emergent SAE, regardless of causality, had been reported in 125/335 patients (37%). Across the studies and regardless of causality or dosing regimen, the most common TEAEs included nausea, fatigue, hyperglycemia, vomiting, diarrhea, stomatitis, and decreased appetite.

3.2.1Study INK128-001

Study INK128-001 is a phase 1, first-in-human, dose-escalation study of single-agent MLN0128 administered to patients diagnosed with advanced solid malignancies, including, but not limited to, colorectal, renal, endometrial, and urothelial tumors. Four dosing schedules are being evaluated (QD, QW, QD×3days per week, and QD×5days per week). Each schedule is administered in 28-day cycles.

As of 09 December 2014, a total of 194 patients had been enrolled. Median age at baseline was 60 years (range, 24-89 years), most (95%) patients are white, and 54% are women. As of data cutoff, 42% had received ≥1 dose of MLN0128 in 2 treatment cycles, while 8% had entered 3 cycles, and 10% had entered 4 cycles. The highest number of cycles that had been initiated as of data cutoff was 46.

The maximum tolerated doses (MTDs) for the 4 schedules investigated in INK128-001 were determined to be 6 mg for QD dosing, 16 mg for QD×3days per week dosing, 10 mg for QD×5days per week dosing, and 40 mg for QW dosing.

Deaths

As of 09 December 2014, a total of 7 patients in this study had died within 30 days of their last dose of study drug as reported to the clinical database. One death was due to ventricular fibrillation and cardiac arrest, 1 was due to pleural effusion, 1 was due to sepsis, 1 was due to respiratory failure, and the remainder was due to disease progression. The event of ventricular fibrillation and cardiac arrest was the only case considered study drug-related; details are provided in section 5.3.1.1. of the IB Ed8.

Serious Adverse Events

As of the clinical database cutoff date, treatment-emergent SAEs had been reported for 82 patients (42%) in this study. The most commonly reported (≥4 patients, overall) preferred terms were stomatitis in 7 patients (4%), pneumonia in 6 patients (3%), abdominal pain or anemia in 5, each (3%), and vomiting, asthenia, or renal failure acute in 4, each (2%).

Treatment-Emergent Adverse Events

Overall, ≥1 TEAE was reported for 194 (100%) of the patients. Across the dosing groups, the most commonly reported TEAEs were nausea or hyperglycemia, which were each reported in 125 patients (64%). The second most common TEAE was vomiting (54% of patients), followed by fatigue (51%).

Across all dosing groups, ≥1 TEAE of severity ≥Grade 3 had been reported for 68% of treated patients as of the clinical data cutoff date. Severity ≥Grade 3 TEAEs, regardless of causality, that were reported in ≥5% of patients as of the data cutoff were hyperglycemia (14% of patients), fatigue or hypophosphatemia (8% each), asthenia (7%), anemia or stomatitis (6% each), and lymphopenia or nausea (5% of patients each).

Events leading to study discontinuation

Of the 194 patients treated in Study INK128-001 as of the clinical data cutoff, 110 (57%) discontinued because of disease progression, 20 (10%) withdrew consent, and 15 (8%) were lost to follow-up or discontinued for other reasons.

A total of 68 AEs led to study discontinuation among 35 patients (18%). Of these events, 32 (47%), including 16 nonserious AEs, were reported as severity Grade 3, and 6 SAEs were Grade 5. No Grade 4 events were reported as resulting in study discontinuation. Most (71%) events were considered study drug-related and had resolved as of the data cutoff date.

A total of 12 preferred terms were reported as leading to discontinuation for >1 patient, including rash (9 patients, including the terms maculopapular [5 patients], rash [2], and rash erythematous or rash pruritic [1 each]), nausea or stomatitis (7 patients each), pruritus or pruritus generalized (4 patients total), and asthenia, fatigue, renal failure/renal failure acute (3 patients, each). Events reported in 2 patients included hyperglycemia, pain or pain in extremity, performance status decreased, and vomiting.

3.2.2 Study INK128-002

Study INK-002 is a completed phase 1, open-label, dose-escalation study of oral MLN0128 administered as a single agent in patients with relapsed or refractory hematologic malignancies (MM or non-Hodgkin lymphoma, including WM). A total of 39 patients received MLN0128 in 1 of 2 regimens: 26 patients received QD doses (range, 2-7 mg) and 13 patients were dosed on a QD×3days per week schedule (range, 9-12 mg). The MTD for the QD schedule was 4 mg. The MTD for the QD×3days per week schedule was 9 mg.

A total of 21 of the patients (54%) in this study were male and 87% were white. The median age at baseline was 61 years (range, 46-85 years).

Deaths
Two patients died during Study INK128-002. One death was due to a subdural hemorrhage, and the other was due to disease progression. Both events were considered by the investigator to be unrelated to MLN0128.

Serious Adverse Events
Treatment-emergent SAEs were reported in Study INK128-002 for 11 patients (28%). No SAE occurred in more than 1 patient. Overall, most SAEs were considered severity Grade 2 or 3. Grade 4 SAEs were reported in 2 patients: hyperviscosity syndrome and hyponatremia were reported in 1 patient in the 2-mg QD dose group (both events resolved); and acute renal failure was reported in 1 patient in the 12-mg QD×3days per week dose group (resolved with sequelae).

No SAEs were considered to be related to MLN0128 treatment, with the exception of 3 events that were reported in 1 patient. This patient experienced Grade 2 pneumonia on Day 58 that resolved without sequelae on Day 60. On Day 121, the same patient experienced SAEs of pneumonia (Grade 2) and hypoxia (Grade 3). The 3 events improved by Day 125 and were resolved as of Day 142. All 3 events were considered by the investigator to be related to MLN0128.

Treatment-Emergent Adverse Events
All patients in Study INK128-002 experienced at least 1 TEAE. Overall, nausea was the most frequently reported preferred term (in 56% of patients), followed by fatigue (49%), hyperglycemia (38%), thrombocytopenia (36%), and diarrhea (28%).

TEAEs of severity ≥ Grade 3 were reported in 24 patients (62%); of these, 18 patients (46%) experienced ≥ Grade 3 events that were considered related to study drug. The most common

study drug-related ≥ Grade 3 TEAEs were thrombocytopenia (in 15% of patients) and fatigue (10%).

Events Leading to Study Discontinuation
Overall, a total of 20 patients (51%) in Study INK128-002 discontinued due to progressive disease, 11 patients (28%) withdrew consent, and 6 (15%) discontinued due to investigator decision or other reasons.
Most events leading to study discontinuation were considered nonserious. Fatigue was reported as resulting in study discontinuation in 2 patients; all other events were reported as leading to study discontinuation in 1 patient only.

3.2.3 Study INK128-003

Study INK128-003 is a phase 1, open-label, dose-escalation study of oral MLN0128 administered in 4-week cycles in combination with paclitaxel in patients with advanced solid malignancies (lung, ovarian, endometrial, breast, pancreatic, prostate, etc).As of the clinical data cutoff date, the treatment period for the primary endpoint had completed and long-term treatment for 1 patient remained ongoing.

In this study, 67 patients received ≥1 study drug dose under 1 of 3 dosing schedules: QW; QD×3days per week; and QD×5days per week. With each regimen, paclitaxel 80 mg/m^2 was dosed on Days 1, 8, and 15 of each cycle. Patients who tested positive for HER2+ received the combination and also received trastuzumab QW.

At total of 57% of the patients are women and 93% are white. At baseline, the median age was 60 years (range, 21-81 years).

On the basis of dose escalation data, 8 mg of MLN0128 on the QD×3days per week schedule was selected for the dose expansion phase in patients with breast cancer. The QD×5days per week and QW schedules were abandoned before MTDs were declared, as they were viewed as being less convenient relative to the QD×3days per week schedule from the perspective of administering the paclitaxel and trastuzumab combination.

Overall in the dose expansion phase, patients entered a median of 3.0 treatment cycles (range, 1-19 cycles) and a mean (SD) of 5.6 (6.07) cycles. The overall median duration of exposure was 7.5 weeks, with a duration over 2-fold greater (11.1 weeks) in the MLN0128 8 mg QD×3days per week HER2- treatment group relative to the MLN0128 8 mg QD×3days per week HER2+ plus trastuzumab group (5.2 weeks). The median cumulative dose was 189.0 mg. Across treatment groups, patients received approximately 75% of their planned dose of MLN0128.

Deaths
As of the clinical data cutoff date, 9 patients in this study had died within 30 days of administration of their last dose of study drug. Of these patients, 6 died due to disease progression, 1 died due to failure to thrive, 1 died due to enlarging tumor mass causing

tracheal compression, and 1 died due to pneumonia. None of the events were considered related to MLN0128.

Serious Adverse Events
As of the clinical data cutoff date, 55 SAEs had been reported among 29 patients (43%) in this study. Overall, 23 patients (49%) reported ≥1 SAE during the Dose Escalation phase and 6 patients (30%) reported ≥1 SAEs during the Expansion phase. The most frequently reported SAEs overall were pneumonia (6 patients), vomiting (2 patients, plus hematemesis in 1 patient), small intestinal obstruction (3 patients), and stomatitis, esophageal carcinoma, sepsis, and failure to thrive in 2 patients each. SAEs reported in most patients (85%) were considered not study drug-related, including all of the fatal events. No SAE event terms were reported in >1 patient in the Dose Escalation phase.

Treatment-Emergent Adverse Events
All patients treated in Study INK128-003 reported at least 1 TEAE. The most common (≥10% of patients) TEAEs, regardless of causality, that were reported as of the clinical database cutoff include fatigue, nausea, and diarrhea, which were reported in 67%, 60%, and 52% of patients, respectively.

Regardless of causality, TEAEs reported in 54 patients (81%) overall were assessed as severity ≥Grade 3. The most commonly reported ≥Grade 3 TEAEs included neutropenia (21% of patients), hypophosphatemia (15%), diarrhea or hyperglycemia (12% of patients each), and fatigue, hypokalemia, and vomiting (10% of patients each).

Events Leading to Study Discontinuation
All but 1 patient had discontinued from MLN0128 treatment in Study INK128-003 as of the clinical data cutoff. Reasons for discontinuation for the other 66 patients included disease progression (54%), patient decision (24%), or ≥1 TEAE (21%). Events reported as leading to study discontinuation for more than 1 patient included fatigue (4 patients) and pneumonia, rash (erythematous or macular), failure to thrive, or vomiting (2 patients, each). A majority (52%) of the events were considered not related to MLN0128. A total of 9 events (43%) were considered serious and 12 were assessed as severity ≥Grade 3, including 3 fatal events. Ten events remained ongoing as of the last contact with the patients.

3.2.4 Study C31001

Study C31001 is a phase 1b/2 study of the safety and efficacy of MLN0128 in combination with exemestane or fulvestrant in women with ER+/HER2– advanced or metastatic breast cancer that has progressed on prior treatment with everolimus in combination with exemestane or fulvestrant. Patients in this study continue receiving their same prior therapy (either exemestane or fulvestrant) at the same dose, in combination with MLN0128.
As of the clinical data cutoff date, 16 patients had received ≥1 MLN0128 dose along with either exemestane (7 patients) or fulvestrant (9 patients). A total of 88% of the women treated as of the data cut were white. At baseline, their median age was 56.5 years (range 42-74 years). Of the original 16 patients, 12 remained ongoing as of data cutoff.

Deaths

As of the clinical data cutoff date, no patient had died within 30 days of administration of their last dose of study drug.

Serious Adverse Events

As of the clinical data cutoff date, 3 treatment-emergent SAEs (ataxia, pneumonitis, and upper respiratory tract infection) had been reported in 3 patients (19%). The SAE of ataxia resulted in a dose delay, and no action was taken in response to the other events. All 3 events were reported as being severity Grade 3 and all had resolved as of the data cut. Only the event of pneumonitis was considered related to study drug.

Treatment-Emergent Adverse Events

The most common (≥12% of patients) TEAEs, regardless of causality, include nausea, fatigue, and diarrhea or stomatitis, which were reported in 69%, 50%, and 44% of patients, respectively.

Regardless of causality, the most common TEAEs considered severity ≥Grade 3 were alanine aminotransferase increased, diarrhea, fatigue, and nausea, each of which were reported in 2 patients

Events Leading to Study Discontinuation

Four patients had discontinued from MLN0128 treatment as of the clinical data cutoff. Reasons for discontinuation were disease progression (2 patients), patient decision (1), and ≥1 TEAEs (1). The TEAE leading to discontinuation was Grade 3 nausea in a patient in the MLN0218+fulvestrant arm. The event was not considered related to study drug and had resolved as of data cutoff.

3.2.5 Study C31002

Study C31002 is a phase 1 open label, single-arm, multicenter study to evaluate the effect of a single dose of 40 mg MLN0128 on the QT/QTc (QT interval corrected for heart rate) in patients with advanced solid tumors. After completing the per-protocol PK/ECG assessments on Cycle 1, Day 3, patients may continue to receive MLN0128 if, in the opinion of the investigator, the patient is deriving clinical benefit, until they experience disease progression. Patients continuing treatment receive MLN0128 30 mg QW in 28-day cycles. As of the clinical data cutoff date, 19 patients had received ≥1 MLN0128 dose in this study and 3 had entered Cycle 2. A total of 53% are women and 74% are white. At baseline, their median age was 63.5 years (range, 46-76 years). Of the original 19 patients, 16 remained ongoing as of data cutoff.

Deaths

As of data cutoff, no reports of events having fatal outcomes had been reported to the clinical database as of data cutoff.

Serious Adverse Events

Serious adverse event information had not been reported to the clinical database as of the data cutoff date.

Treatment-Emergent Adverse Events
The most common (≥10% of patients) TEAEs, regardless of causality, include nausea, fatigue, decreased appetite, and vomiting, which were reported in 53%, 42%, 32%, and 21% of patients, respectively. Information regarding severity of TEAEs had not been reported to the clinical database as of data cutoff.

Events Leading to Study Discontinuation
As of data cutoff, 2 patients had discontinued due to ≥1 AE. The preferred term for 1 event was pelvic pain. The other event had not been coded as of data cutoff; Both events were reported as being Grade 4 in severity, had not yet resolved as of data cutoff, and were not considered study drug-related.

4. UPDATED MANUFACTURING PROCESS

A new MLN0128 capsule containing milled active pharmaceutical ingredient (API) is available for new clinical studies in 1 mg, 3 mg and 5 mg strengths.

The milled API, may result in faster absorption profile with possibly higher maximum concentration (Cmax), which could result in a different safety profile compared to the previous unmilled API capsules. Therefore, ongoing studies (C31001, C31002 and , MLN0128-1004 –A Phase I, open label study to evaluate the safety, tolerability, and pharmacokinetics of MLN0128 as a single agent and in combination with paclitaxel in adult patients with advanced non-hematologuical malignancies-), with the new milled API will determine the recommended phase 2 dose (RP2D) for single agent MLN0128 (QD and QW) and QD×3days per week in combination with paclitaxel, as well as the effect of high-fat meal on the PK of milled API.

5. CLINICAL SUMMARY OF SAFETY

5.1 Special Warnings and Precautions for Use

5.1.1 Insulin and Glucose Levels

Hyperglycemia and hyperinsulinemia are known toxicities associated with inhibition of mTOR and related pathways based on nonclinical studies.

A rise in fasting plasma glucose has been observed as early as 1 to 2 days following oral administration of MLN0128. Daily in-home glucose monitoring and early initiation of treatment of the hyperglycemia are essential. For subject self-monitoring of blood glucose, a finding of fasting blood glucose ≥ 140 mg/dL measured by glucometer would initiate closer monitoring of serum glucose and possible intervention. Subjects with Grade 1 hyperglycemia (fasting serum glucose [FSG] > the upper limit of the normal range ≤ 160 mg/dL) are treated with oral hypoglycemic agents (eg, metformin), and subjects with ≥ Grade 2 hyperglycemia (FSG > 160 mg/dL) are treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. Daily home monitoring and

early treatment, have resulted in good control of glucose levels for the majority of MLN0128-treated subjects who developed hyperglycemia.

5.1.2 Cardiac Effects

Cardiac events (including QT interval corrected for heart rate prolongation and arrhythmias) have been infrequently observed in clinical studies of MLN0128. To date, there has been 1 report of ventricular fibrillation and cardiac arrest postdose that had a fatal outcome and was assessed as related to MLN0128. Routine cardiac monitoring with baseline electrocardiogram (ECG) or multigated acquisition (MUGA) scan and on-study ECGs and physical examination constitute the core cardiac safety monitoring in all MLN0128 studies.

For subjects showing any signs of cardiac instability after MLN0128 dosing, additional monitoring onsite before clinic discharge should be considered.

5.1.3 Renal Function

Elevations in creatinine (regardless of causality) have been observed in subjects receiving MLN0128, all of which have been reversible with drug interruption and/or supportive care with IV hydration. Further evaluation of the renal insufficiency with urine electrolytes suggested a pre-renal etiology with a low fractional excretion of sodium < 1%. However, the adverse event cases were confounded by multiple factors such as nausea, vomiting, hyperglycemia, concomitant medications with GI side effects such as metformin, and hydronephrosis, any of which may have also contributed to dehydration and elevated creatinine. Subjects should be encouraged to drink at least 20 ounces of fluids a day, especially on days requiring fasting (per protocol), with administration of IV fluids in the clinic as indicated to avoid dehydration.

Baseline macroscopic urinalysis and routine serum chemistries along with other safety laboratory assessments are performed in all MLN0128 studies. Additionally, microscopic urinalysis, a 12-hour urine collection, spot urine electrolytes, protein and creatinine, and serum chemistry should be collected at any time when the serum creatinine is ≥ Grade 1, according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, to further evaluate possible etiologies for the renal dysfunction.

5.1.4 Rash

Rash observed in clinical studies of MLN0128 tends to be maculopapular and pruritic and has ranged from Grade 1 to 3. For the most part, rash and pruritus improve with antihistamines, topical steroid creams, and/or dose interruption. Some subjects have required pulse systemic steroids, dose reduction, and/or study treatment discontinuation.

5.1.5 Pneumonitis

Pneumonitis is a known potential risk of mTOR inhibitors. Early recognition, prompt intervention, and a conservative risk management approach are recommended due to pneumonitis that has been observed with rapalog therapy and with MLN0128 administration. Symptoms of pneumonitis will be closely monitored in all MLN0128 study subjects.

5.2 Interactions With Other Medicaments and Other Forms of Interaction

Clinical drug-drug interaction studies have not been conducted with MLN0128. At this time, there are no known drug interactions. In vitro data, including cytochrome P450 induction/inhibition and transporter inhibition studies conducted for MLN0128, suggest a low risk for MLN0128 to precipitate a drug-drug interaction. Although potential drug-drug interactions with MLN0128 cannot be ruled out based on the known metabolism characteristics of MLN0128, the potential risk is considered low.

6. ALISERTIB (MLN8237)

6.1 Aurora A Kinases and the Aurora A Kinase Inhibitor Alisertib (MLN8237)

Alisertib (International Proprietary Name, also known as MLN8237) is a selective small molecule inhibitor of Aurora A kinase that is being developed for the treatment of advanced malignancies. Aurora A kinase (AurA) belongs to a highly conserved family of serine/threonine protein kinases that also includes Aurora B and Aurora C. AurA and Aurora B are expressed in all actively dividing cells, while Aurora C expression is largely restricted to dividing germ cells (15,16). AurA localizes to centrosomes and the proximal mitotic spindle during mitosis where it functions in a diverse set of mitotic processes.

The evidence supporting AurA kinase as a therapeutic target for the treatment of malignancies comes from several sources. First, the AurA kinase gene is amplified, overexpressed, or both in many tumors, including colon, breast, pancreatic, and bladder cancers, as well as certain lymphomas, leukemias, and myeloma (16). AurA overexpression in human cancers has been correlated with increased aneuploidy and centrosome amplification (16,17). Second, forced overexpression of AurA kinase in experimental models results in the transformation of normal cells, suggesting that AurA overexpression may be oncogenic (15). Lastly, in a number of different experimental systems, AurA inhibition leads to mitotic delays and severe chromosome alignment and segregation defects, followed by cell death (18-20). Overall, the essential role of AurA in mitotic progression and its dysregulation in certain cancers makes it an attractive therapeutic target.

Given the obligatory role of mitosis in tumor proliferation, an AurA inhibitor would be expected to have potential applications across a broad range of human tumors. Indeed, alisertib has demonstrated activity against a variety of nonclinical solid tumor and hematological malignancy models grown *in vitro* and *in vivo*, as described below. Alisertib

is also expected to be toxic to proliferating normal tissues, such as the bone marrow, gastrointestinal (GI) epithelium, and hair follicles because any cell that is in mitosis, where AurA is expressed and active, should be susceptible to the effects of an AurA kinase inhibitor.

6.1.1 Alisertib *In Vitro* Studies

Alisertib is an ATP-competitive and reversible inhibitor of AurA kinase *in vitro* with an inhibition constant (Ki) of 0.43 nM. The data from both enzymatic and cell-based assays demonstrated that alisertib is a selective and potent inhibitor of AurA kinase. Alisertib inhibited proliferation of a wide variety of tumor cell lines grown in culture. Moreover, treatment of tumor cell lines with alisertib induced phenotypes consistent with AurA kinase inhibition, including mitotic spindle defects, mitotic delay, and apoptosis (21-24). For further details, refer to the Investigators' Brochure (IB).

6.1.2 Alisertib *In Vivo* Studies

Alisertib demonstrated antitumor activity when administered orally on a daily basis for approximately 21 days (maximal tumor growth inhibition [TGI] > 90%) in several experimental human solid and hematologic tumor models grown as xenografts in immunocompromised mice. The maximally efficacious dose (ED) for each model varied: between 10 and 30 mg/kg if given once daily (QD) and 20 mg/kg if given twice daily (BID). Studies in the HCT-116 colon tumor model showed that less frequent dosing (eg, 5 days on followed by 5 days off) was also efficacious, demonstrating that continuous dosing is not necessary for antitumor activity. A single oral dose of alisertib given to nude mice bearingsubcutaneous HCT-116 human colon tumors resulted in inhibition of activated AurA kinase and an increase in mitotic cells. Therefore, mitotic index (MI) can be used as a pharmacodynamic marker of alisertib in some in vivo settings. The relationship between pharmacokinetics (PK), pharmacodynamics, and efficacy was further studied in HCT-116 xenografts using oral dosing and subcutaneous osmotic mini-pumps. Both a pharmacodynamic response and efficacy (antitumor activity) were achieved using either route of administration. The data from these studies suggest that the maximum pharmacodynamic effect (mitotic accumulation) and efficacy are achieved at steady state plasma concentrations of 1-μM. Moreover, the maximally efficacious oral doses of alisertib in the HCT-116 model (30 mg/kg QD) resulted in plasma concentrations of 1 μM for 8 to 12 hours postdose. Plasma concentrations of alisertib associated with saturating levels of pharmacodynamic and antitumor activity (1 μM) were exceeded at the recommended phase 2 dose (RP2D) of alisertib in patients (50 mg BID).

To determine whether alisertib would enhance the antitumor effects of standard of care agents in solid and hematologic malignancies, nonclinical combination studies were performed. Combination therapy with alisertib and docetaxel resulted in additive or synergistic effects during the dosing period, with prolonged tumor growth delay in multiple solid tumor xenograft models after terminating treatment. These effects were also observed in alternative intermittent dosing schedules. In DLBCL xenograft models, combination therapy with alisertib and rituximab resulted in synergistic, additive, or subadditive effects

depending on the dose and model; however, prolonged tumor growth delays were observed in every case after terminating treatment, and in some cases complete cures were maintained.

6.1.3 Alisertib Safety Pharmacology, Toxicology, and Drug Metabolism

Safety pharmacology studies with alisertib did not identify significant adverse effects in nonclinical studies, including in the central nervous system (CNS) and cardiovascular systems. No alisertib-related effects on clinical signs or physical examination findings indicative of impaired respiratory function (ie, labored or shallow breathing), or microscopic changes in the lungs of animals that survived until scheduled termination, were noted at tolerated doses in Good Laboratory Practice (GLP)-compliant, repeat-dose, toxicology studies. Alisertib exhibited minimal activity against the rapidly activating component of IKr, which is encoded by hERG (IC50 and Ki > 100 μM). Alisertib had *in vitro* activity against the GABAAα1 benzodiazepine binding site (Ki = 290 nM).

The dose-limiting toxicities (DLTs) for alisertib in both rats and dogs after repeat daily oral dosing for 2 cycles (each cycle consisted of 7 consecutive days separated by a 14-day dose holiday) or for 6 cycles (each cycle consisted of 21 consecutive days of dosing separated by a 7-day dose holiday) were consistent with inhibition of AurA kinase by alisertib. Principal findings in toxicology studies in rats and dogs included gastrointestinal (GI) signs, panleukopenia, decreased reticulocyte counts, and increased mitotic figures and apoptosis (single-cell necrosis) in tissues with a high basal cellular replication rate. These findings are indicative of toxicity to rapidly replicating cell populations and are consistent with the outcomes associated with AurA kinase inhibition. No off-target effects were seen in the GLP-compliant toxicology studies.Alisertib was negative in the bacterial reverse mutation assay (Ames assay) both in the absence and presence of Aroclor™ 1254-induced rat liver S9 fractions. In a rat bone marrow micronucleus assay, alisertib was considered to be equivocal for clastogenicity.

Alisertib is metabolized by multiple phase I (cytochrome P450 [CYP]3A4, CYP2C9, CYP2C19, and CYP1A2) and phase II (uridine diphosphate glucuronosyltransferase [UGT] 1A1, 1A3, and 1A8) enzymes. Using human liver microsomes with the appropriate cofactors, the percent contribution of CYP and UGT was calculated to be 13.1% and 86.9%, respectively, showing that CYP isozymes play a minor role in the metabolism of MLN8237. MLN8237 is unlikely to inhibit the 5 major CYP enzymes, 1A2, 2C9, 2C19, 2D6, and 3A4/5 (IC50 > 100 μM) when administered at the projected human efficacious dose. MLN8237 is not a mechanism-based inhibitor of CYP3A4/5. Alisertib inhibited the P glycoprotein (Pgp)-mediated efflux of paclitaxel (Taxol®) in Caco 2 cells with an IC50 of 4.0 μM. Detailed information regarding the nonclinical pharmacology and toxicology of alisertib may be found in the IB.

6.1.4 Alisertib Clinical Experience

As of 29 March 2012, the following company-sponsored alisertib studies were in progress or completed: 6 single-agent phase 1 studies, 3 single-agent phase 2 studies, 1 single-agent

phase 1/2 study, and 3 combination studies. Alisertib for clinical studies is being developed in 2 dosage formulations: Enteric-coated-tablet (ECT) and oral solution (OS). The dose-escalation, phase 1 study, C14007, evaluated multiple dose levels from 10 to 60 mg BID for 7 days in repeat, 21-day cycles and 50 mg BID has been determined to be the MTD.

Alisertib is structurally related to the benzodiazepines (BZD) (eg, diazepam, lorazepam) and also has activity against the GABAAα1 BZD receptor. BZD-like effects (eg, somnolence, confusion, memory loss) have been observed to be associated with the onset of maximal plasma concentration (eg, Tmax [time to maximum plasma concentration]). CNS effects associated with peak plasma levels have been generally managed by administration of divided doses (eg, BID administration), although dose reductions have sometimes been required. While CNS effects attributed to alisertib were also generally reversible and manageable by dose delay or reduction, the causal relationship, and thus optimal approach to management, were sometimes confounded by diverse causes including, but not limited to, concomitant medications (eg, narcotic analgesics, antianxiety medications), comorbidities (eg, infection, anemia, electrolyte abnormalities), or progressive malignancy (eg, brain metastases). The clinical experience with alisertib includes treatment with multiple doses and schedules and is summarized in the IB.

6.1.5 Alisertib Pharmacokinetics

Upon oral administration to patients with advanced nonhematologic malignancies, absorption of alisertib was fast, with peak plasma concentrations generally achieved by 3 hours postdose. Negligible urinary excretion of alisertib was observed in humans. The renal clearance of alisertib in humans was less than 0.1% of apparent oral clearance. Steady-state plasma exposures of alisertib increased in an approximately dose-proportional manner over the range of 5 to 200 mg/day in patients with advanced solid tumors. Overall mean steady state terminal half-life following multiple-dose administration in patients with nonhematologic malignancies was approximately 22 hours. The overall mean peak/trough ratios were 2.6 and 5.0 for BID and QD dosing, respectively. The overall mean accumulation ratios were 2.8 and 1.9 for BID and QD dosing, respectively. Pharmacokinetic steady-state conditions were approximately achieved by Day 7 following daily oral administration. The PK properties of alisertib in patients with hematologic malignancies were generally consistent with those observed in patients with nonhematologic malignancies. Based on PK and genotype data in patients with nonhematologic malignancies, there was a substantial overlap in exposures (dose-normalized steady-state area under the plasma concentration versus time curve [AUC]) of alisertib in patients with 0, 1, or 2 copies of the UGT1A1 *28 allele, indicating the lack of readily apparent effects of UGT1A1 genotype on alisertib systemic exposure.

Clinical pharmacokinetic data available as of 20 April 2012 are summarized in the IB. Upon oral administration to patients with advanced nonhematologic malignancies, absorption of alisertib was fast, with peak plasma concentrations generally achieved by 2 hours post dose. Negligible urinary excretion of alisertib was observed in humans. The renal clearance of alisertib in humans was less than 0.1% of apparent oral clearance. Steady-state plasma exposures of alisertib increased in an approximately dose proportional manner over the

range of 5 to 200 mg/day in patients with advanced solid tumors. Overall mean steady-state terminal half-life following multiple-dose administration in patients with nonhematologic malignancies was approximately 22 hours. The overall mean peak/trough ratios were 2.6 and 5.0 for BID and QD dosing, respectively. The overall mean accumulation ratios were 2.8 and 1.9 for BID and QD dosing, respectively. Pharmacokinetic steady-state conditions were approximately achieved by Day 7 following daily oral administration.

Based on the results of a population PK analysis in 294 adult cancer patients, the apparent oral clearance of alisertib CL/F was unaffected by age, body weight, BSA, or the UGT1A1 genotype (number of *28 alleles). These results support the use of a common fixed starting dose of alisertib independent of UGT1A1 genotype status, age or body size in the adult patient population, in the ongoing and planned clinical trials.

The absolute bioavailability of alisertib in humans has not been determined; however, the single-dose pharmacokinetics of a prototype oral solution formulation of alisertib (25-mg dose) were characterized in a cross-over relative bioavailability evaluation in Study C14010 in 15 patients with nonhematologic malignancies.

The effect of a standardized high-fat meal on the PK of single dose alisertib administered as a 50-mg strength was evaluated in 14 patients with advanced solid tumors. The lack of an effect of food on alisertib AUCinf observed in this study supports the conclusion of the lack of a clinically meaningful effect of food on the PK of alisertib. The results of this study, therefore, support a recommendation that alisertib may be dosed without regard to the timing of meals in future clinical studies, unless otherwise specified in the clinical study protocol.

6.1.6 Alisertib Potential Risks and Benefits

Seven-hundred fourteen patients (excluding 13 patients from a company-sponsored, non-US IND study in Japan) have been treated with alisertib as of 29 March 2012. Clinical safety data includes experience from patients who received multiple cycles followed by treatment free periods between each cycle, and from patients who reduced or discontinued treatment. Based on the available clinical data, drug abuse, dependency, and drug withdrawal effects were not observed.

To date, the observed risks associated with alisertib treatment, as detailed in the Safety Management Attachment of the IB, include: (1) reversible myelosuppression including leukopenia, neutropenia, febrile neutropenia, lymphopenia, thrombocytopenia, and anemia; (2) GI toxicity including stomatitis/mucositis/oral pain, nausea, vomiting, anorexia, abdominal pain, dyspepsia, diarrhea, and dehydration; (3) sedation, somnolence, confusional state, disorientation (and associated memory loss), and gait disturbances; (4) alopecia; (5) asthenia/fatigue; (6) fever, (7) infection, (8) abnormal liver function tests (including aspartate transaminase [AST], alanine transaminase [ALT], bilirubin, alkaline phosphatase [ALP], and gamma glutamyl transferase [GGT]), and (9) rash, which may include bullous dermatitis, and palmar-plantar erythrodysaesthesia syndrome.While these toxicities are potentially associated with risk or discomfort to the patient, they are anticipated to be

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

Because alisertib inhibits AurA kinase, it is possible that alisertib may interfere with cancer growth and cause cancer cell death. Preclinical results indicate that alisertib is not a major substrate for efflux mechanisms that have been associated with cross-resistance between some types of anticancer agents. Thus, alisertib has potential through a potentially non-cross resistant pathway as compared to other agents the patients may have received. The clinical utility of these effects will be investigated in current and future studies.

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

6.2 Risk of MLN0128 and Alisertib Combination Therapy

Overlapping toxicity is not expected with the combination of MLN0128 and alisertib, however, the risk of increased toxicity with combination therapy is possible. Dose limiting adverse events observed with MLN0128 treatment include mucositis, hyperglycemia, diarrhea and fatigue. Dose limiting adverse events observed with alisertib treatment include myelosuppression and CNS depression. As described in Section 10.1 and Table 1, dosing will begin below the MTD for each agent in the dose escalation cohort. Patients will be monitored for toxicity and management guidelines are provided to facilitate early detection and rapid, appropriate management of toxicity.

7. STUDY RATIONALE

7.1 Alisertib and MLN0128 in TNBC

Metastatic TNBC is a biologically heterogeneous disease and the development of active targeted therapies in conjunction with effective biomarker selection strategies is an area of unmet clinical need (25,26). AurA plays a critical role in mitosis including functions in chromosome alignment, spindle formation, and cytokinesis (27,28). It functions as an oncogene through the promotion of genetic instability (15) and over-expression of AurA has been linked to inferior outcomes in patients with early stage breast cancer (29). Aurora kinase inhibitors (AKIs) are a promising class of drugs for the treatment of TNBC based on their anti-mitotic mechanism of action and the high mitotic index observed in TNBC. (30).

Alisertib is an orally bioavailable, second-generation selective AKI with broad antiproliferative and anti-tumor activity in preclinical *in vitro* and *in vivo* TNBC models (23). Alisertib treatment resulted in a G2/M cell cycle arrest and the induction of apoptosis in a subset of p53 wildtype and mutant sensitive TNBC cell lines (23). *TP53* is the most commonly mutated gene in TNBC with an incidence of approximately 85% (31). While the majority of mutations are missense mutations in the DNA binding domain, more complex mutations (ie frameshift and nonsense mutations) occur at a higher frequency in TNBC as compared to luminal breast cancers (32). Mutations in p53 may abrogate its tumor suppressor function resulting in impairment of cell cycle arrest, DNA repair and apoptosis

(33). AurA over-expression may lead to increased p53 degradation via phosphorylation of p53 at Ser315, leading to increased ubiquitination by MDM2 (34). Furthermore, silencing of AurA results in stabilization of p53 and a characteristic G_2/M cell cycle arrest (34).

Sensitivity to the pro-apoptotic activity of alisertib in TNBC is mediated by both p53 and the p53 family member p73. Knock-down (KD) of either p53 or p73 using shRNA in the p53 wildtype CAL-51 TNBC cell line led to an increase in resistance to the antiproliferative and proapoptotic effects of MLN8237 (23). This shift to resistance was associated with an increase in senescence associated-β-galactosidase (SA-β-gal) activity and phenotypic features consistent with senescence (23). These findings support the induction of senescence as a mechanism for resistance to the anti-apoptotic effects of MLN8237 in cells lacking functional p53 or p73.

Alisertib is active against TNBC xenograft and patient-derived tumor xenograft (PDX) models where apoptosis is observed in sensitive models as detected by cleaved caspase-3 staining (23). Senescence and upregulation of genes in the PI3K/AKT/mTor pathway were observed in PDX models treated with alisertib to resistance. This finding is consistent with an emerging body of literature supporting a critical role for mTOR in oncogenic and DNA-damage induced senescence (35).

Based on the role of mTOR in senescence and upregulation of the PI3K/AKT/mTor pathway in TNBC models resistant to AKIs, we investigated the combination of alisertib and the Torc1/2 inhibitor MLN0128 in TNBC PDX models. The combination of MLN8237 and MLN0128 resulted in greater TGI as compared to either agent alone (Figure 3A), accompanied by an increase in apoptosis as measured by BAX and DR5 expression (Figure 3B) and a decreased senescence as evaluated by SA-β-gal and phenotypic changes (Figure 3C).

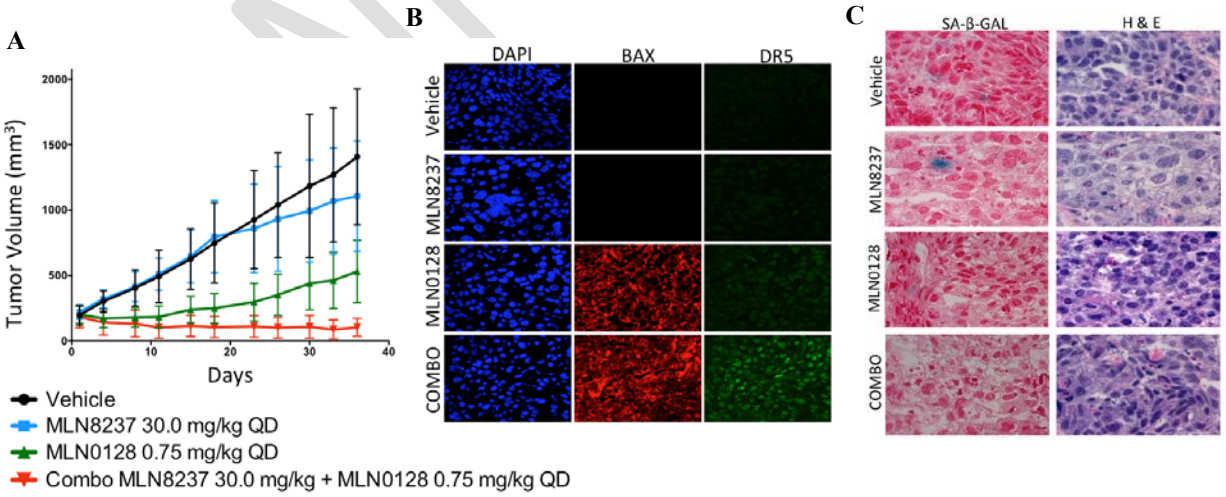


Figure 3. ***In vivo*****, combination therapy with alisertib (MLN8237) and MLN0128 significantly inhibits growth over monotherapies. A.** Tumor growth of TNBC PDX CU_TNBC_005 in vehicle or experimental agent-treated mice (n = 10/group) were plotted. Combination therapy significantly enhances tumor growth inhibition compared to vehicle ($p < 0.0001$) or single agents ($p < 0.0001$). **B**. Cotreatment with alisertib (MLN8237) and MLN0128 enhances expression of pro-apoptotic proteins BAX and DR5 in tumors excised at Day 38. **C.** Treatment with MLN8237 induces SA-β-gal activity (blue stain) that is not observed with combination treatment.

The purpose of this study is to evaluate the combination of alisertib and MLN0128 in patients with advanced solid tumors refractory to standard treatment followed by an expansion cohort of patients with metastatic TNBC and other solid tumors with exploratory correlative studies in select cohorts. The starting dose of MLN0128 is 1 mg PO daily with continuous dosing. This dose is 75% lower than the MTD of single agent milled MLN0128 (4 mg) PO daily when administered in a continuous dosing schedule. The starting dose of alisertib is 30 mg PO BID. This dose is in the biologically active dose range and is 40% lower than the MTD of single agent alisertib (50 mg PO BID Days 1-7 repeat every 21 days).

7.2 Correlative Studies

Serial tumor biopsies will be performed in the Expansion Cohort Group 1 and Group 2. Tumor tissue will be obtained prior to initiating study drug treatment, Cycle 1 Day 7, Cycle 2 Day 7 and at the time of progression in patients with an initial response to treatment. Tissue samples will be processed, assayed and analyzed at the University of Colorado Cancer Center. Testing will include immunohistochemistry (IHC), SA-β-gal staining, gene expression profiling and DNA mutation testing. Other markers may be investigated depending on ongoing preclinical work.

Functional Imaging with diffusion-weighted MRI (DWI) and 5-fluoro-deoxy-glucose-PET (FDG-PET) will be performed at the University of Colorado Cancer Center in a subset of patients enrolled in Dose Expansion Groups 1 and 2 depending on the presence of tumor lesions amenable to imaging evaluation. Oncologic imaging has evolved and now represents a key diagnostic platform for cancer diagnosis and treatment. In addition to capabilities in determining tumor size, molecular and physiologic imaging is now available in order to assess tumor metabolism, physiology and molecular targets non-invasively in real time. As such, Positron Emission Tomography (PET) plays a crucial role in assessing tumor metabolic aggressiveness by determining uptake rates of the 18F-radioactive glucose analogue (FDG) which is up-regulated in TNBC and is a sensitive marker for treatment response to novel targeted agents. Tumor cellularity can be assessed by measuring water tissue properties by diffusion-weighted MRI (DWI) which is clinically used to assess tumor response to chemotherapy as a marker of apoptosis (36,37). These studies will be performed and analyzed by Natalie Serkova, PhD (Associate Professor of Anesthesiology, Pharmacology and Radiology; Director, Colorado Clinical Translational Science Institute Imaging Core) and her staff.

8. STUDY OBJECTIVES

8.1 Primary Objectives

- To determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of the combination of MLN0128 and alisertib in adult patients with advanced solid tumors.

8.2 Secondary Objectives

- To determine the safety profile and tolerability of the combination of MLN0128 and alisertib in adult patients with advanced solid tumors.
- To determine the pharmacokinetics of MLN0128 and alisertib in the combination.
- To evaluate the pharmacodynamic effects of MLN0128 and alisertib in serial tumor biopsies and blood samples in patients with metastatic TNBC and other solid tumors enrolled in the expansion cohort at the MTD.
- To estimate the objective response rate using RECIST 1.1 and time to progression in patients with advanced solid tumors treated with MLN0128 and alisertib.

8.3 Tertiary/Exploratory Objectives

- To explore biomarkers predictive of response to MLN0128 and alisertib including the investigation of mechanisms of acquired resistance to treatment in patients with metastatic TNBC and other solid tumors treated in the expansion cohort at the MTD.
- To evaluate the pharmacodynamic effect of the combination of MLN0128 and alisertib on cellular metabolism using functional imaging with FDG-PET (5-fluoro-deoxy-glucose-PET) and diffusion weighted magnetic resonance imaging (DWI-MRI).

9. STUDY ENDPOINTS

9.1 Primary Endpoints

DLTs are defined according to the AE profile observed during the DLT assessment window of up to 28 days following the first dose of MLN0128 (Cycle 1 Day -7 to Cycle 1 Day 21) in the Dose Escalation portion of the trial (see Sections 10.1, 10.2 and 12.2). Toxicity will be graded according to the NCI CTCAE Version 4.03.

9.2 Secondary Endpoints

- Safety: Adverse events according to the NCI CTCAE v.4.03 that occur after the first dose of study drug.
- Pharmacokinetics: PK analysis will be performed only to evaluate the effects of MLN0128 and alisertib on the disposition of each other. PK analysis will be obtained only during Cycle 1 of the Dose Escalation cohort.

- Efficacy: Objective response rate based on imaging with CT or MRI will be evaluated using RECIST 1.1 criteria. Time to progression as defined as the time from the first day of treatment to the first observation of disease progression will be determined.

9.3 Tertiary/Exploratory Endpoints

- Serial tumor biopsies will be performed in the Expansion Cohort Group 1 and Group 2. Tumor tissue will be obtained prior to initiating study drug treatment, Cycle 1 Day 7, Cycle 2 Day 7 and at the time of progression in patients with an initial response to treatment. Tissue samples will be tested and analyzed at the University of Colorado Cancer Center for the following:
    a. pHH3, Ki67, pAurA, p16, p4E-BP1, pS6 and pAKT (Immunohistochemistry [IHC])
    b. p53 and mTor pathway target gene expression (gene expression profiling and RT-PCR)
    c. Senescence-associated beta-galactosidase staining (SA-β-gal)
    d. DNA mutation testing (baseline and time of progression only, Ion Ampliseq Cancer Hotspot Panel or similar platform depending on advancement of technology at the time of analysis)
    e. Possibly other markers depending on ongoing preclinical work
- Functional Imaging with diffusion-weighted MRI (DWI) magnetic resonance imaging and 5-fluoro-deoxy-glucose-PET (FDG-PET) will be performed at the University of Colorado Cancer Center in a subset of patients enrolled in Dose Expansion Groups 1 and 2 depending on the presence of tumor lesions amenable to imaging evaluation. These studies will be performed and analyzed by Natalie Serkova, PhD (Associate Professor of Anesthesiology, Pharmacology and Radiology; Director, Colorado Clinical Translational Science Institute Imaging Core) and her staff.

10. STUDY DESIGN

10.1 Overview of Study Design

This is a Phase Ib open-label, single institution, dose-escalation study designed to evaluate the safety, tolerability, and pharmacokinetics of MLN0128 administered by mouth (PO) in combination with alisertib administered PO to patients with advanced solid tumors and previously treated metastatic TNBC and other solid tumors in an expansion cohort. The initial schedule of MLN0128 administration will be once daily with continuous dosing. If this schedule is not tolerable in combination with alisertib, other schedules may be considered including once weekly dosing or other interrupted schedules. The initial schedule of alisertib administration will be twice daily for 7 days of a 21 day cycle. If this schedule is not tolerable in combination with MLN0128 then other interrupted dosing schedules may be considered.

The dose escalation portion of the trial will be conducted using a standard 3 + 3 dose-escalation design in patients with advanced solid tumors refractory to standard therapies or where no standard therapy exists (see also Figure 1, Table 1 and Section 10.2). Once the

maximum tolerated dose (MTD) / recommended phase II dose (RP2D) is identified, the dose expansion portion will be conducted in patients with previously treated metastatic TNBC and other solid tumors. Exploratory correlative studies will be conducted in the expansion cohort including: evaluation of pharmacodynamics markers in serial tumor biopsies and blood samples, exploration of predictive biomarkers using fresh and archival tissue samples, and evaluation of cellular metabolism using functional imaging.

A total of 30 patients will be treated in the dose-expansion cohort at the MTD/RP2D (see Figure 2 for dose expansion cohort schema). All patients in the expansion cohort group 1 and 2, will be required to undergo fresh tumor biopsy prior to initiating treatment, Cycle 1 Day 7, and Cycle 2 Day 7. In expansion cohort Group 1, single agent alisertib will be administered at the MTD on Days 1-7 and MLN0128 will be administered on Days 8-21. In Cycle 2 and beyond, dosing with both agents will begin on Day 1. In expansion cohort Group 2, MLN0128 will be administered at the MTD in Cycle 1 Days 1-28 and alisertib will be administered at the MTD on Days 8-15. An attempt will be made to obtain a repeat tumor biopsy at the time of progression in patients with an initial response to treatment in group 1 and 2.

Table 1. Planned Dose Levels

Dose Level	Number of Patients	MLN0128[1]	Alisertib[2]
-1	3-6	1 mg PO daily	20 mg PO BID
1(Starting Dose)	3-6	1 mg PO daily	30 mg PO BID
2	3-6	2 mg PO daily	30 mg PO BID
3	3-6	2 mg PO daily	40 mg PO BID
4	3-6	3 mg PO daily	40 mg PO BID
5	3-6	3 mg PO daily	50 mg PO BID
6	3-6	4 mg PO daily	50 mg PO BID
MTD	20	TBD	TBD

1. MLN0128 will be administered orally once daily with continuous dosing. A single dose of MLN0128 will be administered on Cycle 1 between Day -7 to Day -3. Continuous dosing in Cycle 1 during the Dose Escalation Cohort will begin on Cycle 1 Day 2.
2. Alisertib will be administered orally twice daily days 1-7 of each 21 day cycle. A single dose of alisertib will be administered on Cycle 1 Day 1 and BID dosing will be initiated on Cycle 1 Day 2.

Based on an efficacy signal observed in a patient with metastatic pancreatic adenocarcinoma, an expansion cohort of 10 patients with previously treated, locally advanced or metastatic pancreatic adenocarcinoma will be treated at the MTD/RP2D.

All patients will be followed carefully for adverse events during the study period and for at least 30 days after the last dose of MLN0128 or alisertib or until initiation of another cancer treatment. Additionally, patients with unresolved adverse events or abnormal laboratory values related to MLN0128 or alisertib may be contacted by telephone for follow-up of these events. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Blood samples will be taken before and at predetermined times after a single dose of MLN0128 on Cycle 1 Day -7 to Day -3, after a single dose of alisertib on Cycle 1 Day 1, and after

combination treatment on Cycle 1 Day 7 and Day 1 of subsequent cycles to determine the PK properties of MLN0128 and alisertib.

Disease status will be assessed using RECIST 1.1. Patients will undergo tumor assessments at screening, at the end of Cycle 3 and every three cycles thereafter, or as clinically indicated. Tumor status will be categorized as a complete response, partial response, stable disease, or progressive disease per RECIST 1.1. An objective response will be considered confirmed once the same assessment is made by repeat evaluation $\geq$ 4 weeks after the initial documentation, per RECIST 1.1.

Protocol treatment will be discontinued in patients who experience disease progression or unacceptable toxicity or who are not compliant with the study protocol. Treatment with MLN0128 or alisertib alone may be continued if the other agent is discontinued for unacceptable toxicity related to only one study agent. A study completion visit will be performed within 30 days after the last dose of protocol treatment in all patients.

In addition to the protocol, the Investigator should refer to the associated Investigator's Brochure, the Study Procedures Manual, and the appendices of this clinical study protocol for further information regarding this investigational product or details of the procedures to be followed during the course of this study.

10.2 Dose Escalation Cohort

The starting dose for MLN0128 is 1 mg (milled formulation) PO once daily with continuous dosing. This dose is 75% lower than the MTD of MLN0128 in the Ph1b/2 study C31001 which is 4 mg (milled formulation). The starting dose of alisertib is 30 mg PO BID Days 1-7 repeat every 21 days. This dose is 40% lower than the MTD of alisertib (50 mg) for this dosing schedule. During Cycle 1 in the Dose Escalation Cohort only, a single dose of MLN0128 will be administered on Cycle 1 between Day -7 to -3 to allow for single agent MLN0128 PK analysis. Continuous dosing with MLN0128 will begin Cycle 1 Day 2. A single dose of alisertib will be administered on Cycle 1 Day 1 to allow for single agent alisertib PK analysis and BID dosing with alisertib will begin on Cycle 1 Day 2.

DLTs will be assessed during the DLT assessment window of up to 28 days following the first dose of MLN0128 (Cycle 1 Day -7 to Cycle 1 Day 21). Patients who withdraw from the study prior to completing the DLT assessment window for any reason other than a DLT will be replaced. In addition, patients who miss a total of $\geq$ 3 days of scheduled dosing for MLN0128 or alisertib during the DLT assessment window for reasons other than a DLT will be replaced. See Section 12.2 for DLT definition.

After dosing has been completed in each cohort, data pertaining to dose-escalation decisions for MLN0128 and alisertib will be reviewed by the Sponsor Investigator, Clinical Trial Manager and at least 2 other Phase I Oncologists (co-investigators). Available adverse event data, laboratory assessments, ECGs, dose administration logs and PK parameters (when available) will be used to determine whether dose escalation should continue and, if so, at what dose level and schedule (see Table 1). The dose escalation schema may be altered if toxicity is observed related to one agent which would favor escalation of the other agent.

Dose escalation will procede in accordance with the following rules (see Figure 1):

- A minimum of 3 patients will be treated in each cohort.
- If 0 patients experience a DLT in a cohort, dose escalation will proceed.
- If 1 of the first 3 patients in a cohort experiences a DLT then 3 additional patients will be enrolled in that cohort.
- If less than 1/3 of the evaluable patients in a cohort experience a DLT then escalation will proceed
- If 1/3 or more evaluable patients in a cohort experience a DLT, then the MTD has been exceeded and the preceding dose level will be expanded to 6 evaluable patients (If 6 patients have not already been evaluated at that level). Intermediate dose levels may be evaluated at the discretion of the Sponsor Investigator after discussion with the study team.
- If the MTD is exceeded in the first dosing cohort, lower doses or alternate schedules of MLN0128 or alisertib will be evaluated as guided by observed toxicities.
- If the MTD is exceeded at a given dose level then the next highest dose at which less than 1/3 of at least 6 evaluable patients experiences a DLT will be declared the MTD.
- If fewer than 1/3 of at least 6 evaluable patients experiences a DLT at the highest planned dose level then this dose level will be declared the RP2D.

10.3 Study Procedures

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow. If a subject has an unscheduled clinic visit, data from procedures performed, per standard of care, may be collected and used for research purposes at the investigators discretion.

10.3.1 Informed Consent

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

10.3.2 Patient Demographics

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

10.3.3 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 the disease. ER, PR and HER2 status should be collected for breast cancer patients.

10.3.4 Physical Examination

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

Physical examination findings within the following categories will be assessed:

- HEENT
- Pulmonary
- Cardiovascular
- GI/abdomen
- Extremities
- Neurological
- Skin and hair

10.3.5 Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature and weight. Height will be measured only during screening.

10.3.6 ECOG Performance Status

The ECOG Performance Status (refer to Appendix 1) will be assessed at the times specified in the Schedule of Events.

10.3.7 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from first dose of study drug through 30 days after the last dose. See Section 12.5 and Section 12.6 for a list of medications and therapies that are prohibited and/or permitted during the study.

Clinical laboratory evaluations will be performed locally. Blood and urine samples for analysis will be obtained as specified in the Schedule of Events. Results of hematology and clinical chemistry safety labs must be available and reviewed by the investigator before enrollment and initial administration of study drug. Serum pregnancy tests will be performed in women of child bearing potential as specified in the Schedule of Events. A positive pregnancy test prior to dosing will exclude the patient from enrollment in the study. Values for the following parameters will be obtained:

HEMATOLOGY	CLINICAL CHEMISTRY	URINALYSIS
Hemoglobin Hematocrit Platelet Count White Blood Cell Count Differential, including: Neutrophils Lymphocytes Basophils Monocytes Eosinophils	Total protein Albumin Creatinine Bilirubin (total) Alkaline phosphatase AST(SGOT) ALT (SGPT) Glucose Calcium Phosphorus Bicarbonate Chloride Sodium Potassium Magnesium	Color/appearance Specific gravity pH Protein (qualitative) Glucose (qualitative) Ketones (qualitative) Bilirubin (qualitative) Blood (qualitative) Standard microscopic examination if above parameters are abnormal
COAGULATION TESTS		**OTHER**
Prothrombin time (PT) or International Normalized Ratio (INR) Partial thromboplastin time (PTT)		Serum Pregnancy Test Fasting Serum Glucose (patients are required to fast overnight as defined as nothing except water and/or medications after midnight or for a minimum of 8 hours) HbA1C
FASTING LIPID PROFILE		
Total cholesterol Triglycerides High-density lipoprotein cholesterol (HDL) Low-density lipoprotein cholesterol (LDL)		

10.3.8 In-home fasting glucose monitoring

Patients will be instructed to complete daily glucose monitoring at home after fasting overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) for each of these measurements. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded into source documents.

10.3.9 Pharmacokinetic measurements

Pharmacokinetic studies will be performed at the timepoints outlined in the Schedule of Events including on the day of on treatment tumor biopsies. Instructions for preparation, completion, and shipment of PK samples are included in the Study Procedure Manual.

10.3.10 Tumor Biopsies

All patients in the expansion cohort group 1 and 2, will be required to undergo fresh tumor biopsy prior to initiating treatment, Cycle 1 Day 7, and Cycle 2 Day 7 as outlined in the Schedule of Events and Figure 2. Tumor biopsies will be performed as per local institutional guidelines. An attempt should be made to obtain a repeat tumor biopsy at the time of progression in patients with an initial response to treatment.

Instructions for preparation, completion, and processing of tumor biopsies are included in the Study Procedure Manual.

Tumor biopsies will not be performed in the pancreatic adenocarcinoma expansion cohort.

10.3.11 Functional Imaging

DWI-MRI and FDG-PET/CT will be obtained on select patients as outlined in the Schedule of Events. Instructions for functional imaging are included in the Study Procedure Manual.

10.4 Number of Patients

The total number of patients enrolled in the Dose Escalation Cohort will depend on the number of dose cohorts required to identify the MTD. Escalation to the next dose cohort will depend on the probability of DLT at a given dose. When 1 of 3 patients develops a DLT and the cohort is expanded to 6 patients, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of < 10%.

A maximum of 6 patients can be enrolled at each dose level. With 6 potential dose levels and an Expansion Cohort of 30 patients, the maximum number of patients that can be enrolled is 56 and the minimum number is 6. Patients will be considered enrolled on the first day of MLN0128 or alisertib study drug treatment.

10.5 Duration of Study

Patients will continue to receive treatment with MLN0128 and alisertib until they experience disease progression or have an unacceptable drug-related toxicity. There is no maximum duration of treatment. The study will be terminated 6 months after the last patient completes the End-of-Treatment (EOT) study visit.

11. STUDY POPULATION

11.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Dose Escalation Cohort: Patients must have a diagnosis of a histologically confirmed solid tumor that is incurable and refractory to standard therapy or for which no standard therapy exists.

3. Dose Expansion Cohort Group 1 and 2: Patients must have a diagnosis of histologically confirmed metastatic TNBC defined as negative for estrogen receptor,

progesterone receptor and HER2. Patients must have received either adjuvant chemotherapy or first line chemotherapy for metastatic disease. Negative for Estrogen and Progesterone Receptor includes the following:

- Local Pathology report classifies them as negative
- Allred Score of 2 or below
- <1% positive staining

Subjects with solid tumor types other than TNBC may also be enrolled after discussion with the Sponsor. These subjects must have a diagnosis of a histologically confimed solid tumor that is incurable and refractory to standard therapy or for which no standard therapy exists.

4. Pancreatic Cancer Cohort: Patients must have a diagnosis of locally advanced or metastatic pancreatic adenocarcinoma previously treated with or not a candidate for standard of care systemic therapy.

5. Dose Expansion Cohort Group 1 and 2: At least one tumor lesion amenable to repeat core needle biopsy or punch biopsy without unacceptable risk of a major procedural complication.

6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (See Appendix 1)

7. Three weeks or 5 half-lives (whichever is shorter) from previous systemic anticancer therapy; at least 4 weeks from major surgery and recovered; at least 2 weeks from palliative radiation and recovered. No more than 450 mg/m^2 cumulative dose of doxorubicin or equivalent anthracycline dose is allowed.

8. All acute treatment-related toxicities from prior therapy must have resolved to Grade ≤ 1 prior to study entry excluding alopecia.

9. For women:

   - Postmenopausal for at least 1 year before the screening visit, OR
   - Surgically sterile, OR
   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug OR agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence [e.g, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception

   For men, even if surgically sterilized (ie, status post-vasectomy), they must:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR agree to practice true abstinence, when this is in line with the preferred and usual lifestyle

of the patient (Periodic abstinence [e.g, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception

- Agree not to donate sperm during the course of this study or 120 days after receiving their last dose of study drug

10. Screening clinical laboratory values as specified below:

    a) Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; platelet count ≥ 100 x 10^9/L; hemoglobin ≥ 9 g/dL. Values must be obtained without the need for myeloid growth factor support, platelet or PRBC transfusion support within 14 days.

    b) Hepatic: total bilirubin ≤ 1.5 x upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases are present);

    c) Renal: Creatinine ≤ 1.5 X ULN or creatinine clearance ≥ 50 mL/min based either on Cockroft-Gault estimate or based on urine collection (12 or 24 hour)(Appendix 2);

    d) Metabolic: Glycosylated hemoglobin (HbA1c)<7.0%, fasting serum glucose (≤ 130 mg/dL) and fasting triglycerides ≤ 300 mg/dL;

    e) For patients undergoing serial tumor biopsies, INR and activated partial thromboplastin time (PTT) must be within 1.5 X the upper limit of normal.

11. Left ventricular ejection fraction (LVEF) ≥ LLN of the institutional standard of normal as measured by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) within 4 weeks prior to first study drug administration.

12. Ability to swallow oral medications.

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

14. Patients who have a history of brain metastasis are eligible for the study provided that all the following criteria are met:

a) Brain metastases which have been treated

b) No evidence of disease progression for ≥ 4 weeks or hemorrhage after treatment

c) Off-treatment with dexamethasone for 2 weeks before administration of the first dose of MLN0128

d) No ongoing requirement for dexamathasone or anti-epileptic drugs

11.2 Exclusion Criteria

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

1. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study.

2. Known human immunodeficiency virus infection.

3. Radiation therapy to more than 25% of the bone marrow. Whole pelvic radiation is considered to be over 25%.

4. Known history of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness, such as severe chronic obstructive pulmonary disease; requirement for supplemental oxygen.

5. Systemic infection requiring IV antibiotic therapy within 14 days preceding the first dose of study drug, or other severe infection.

6. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.

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

8. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

9. Breast feeding or pregnant.

10. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128. In addition, patients with enteric stomata are also excluded.

11. Treatment with any investigational products within 3 weeks before the first dose of study drug.

12. History of any of the following within the last 6 months before administration of the first dose of the drug:

    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures
    - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia)
    - Placement of a pacemaker for control of rhythm
    - New York Heart Association (NYHA) Class III or IV heart failure (See Appendix 3)
    - Pulmonary embolism

13. Significant active cardiovascular or pulmonary disease including:

    - Uncontrolled hypertension (i.e., systolic blood pressure >180 mm Hg, diastolic blood pressure > 95 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed.
    - Pulmonary hypertension
    - Uncontrolled asthma or O_2 saturation < 90% by arterial blood gas analysis or pulse oximetry on room air
    - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement

- Medically significant (symptomatic) bradycardia
- History of arrhythmia requiring an implantable cardiac defibrillator
- Baseline prolongation of the rate-corrected QT interval (QTc) (e.g., repeated demonstration of QTc interval > 480 milliseconds, or history of congenital long QT syndrome, or torsades de pointes)

14. Treatment with strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, CYP2C19 or CYP2C19 within 1 week preceding the first dose of study drug.

15. Patients receiving systemic corticosteroids (either IV or oral steroids, excluding inhalers or low-dose hormone replacement therapy) within 1 week before administration of the first dose of study drug.

16. Daily or chronic use of a proton pump inhibitor (PPI) and/or having taken a PPI within 7 days before receiving the first dose of study drug

17. For patients undergoing serial tumor biopsies, known bleeding diathesis or history of abnormal bleeding or require anti-coagulation therapy which cannot be interrupted for biopsy.

12. STUDY DRUG

12.1 Study Drug Administration

All protocol-specific criteria for administration of MLN0128 and alisertib must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

MLN0128 will be administered orally on an empty stomach once daily. Patients should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose. Alisertib will be administered orally twice daily for 7 days of a 21 day dosing schedule. The doses of MLN0128 and alisertib will be determined as outlined in Sections 10.1 and 10.2. On days when MLN0128 and alisertib are both administered, the first dose of alisertib should be administered in the morning with the MLN0128 dose. The second dose of alisertib should be administered approximately 12 hours later with or without food.

Patients should be instructed to take their study medication at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. If a patient does not take their MLN0128 or alisertib dose within the time frame specified (+/- 8h for MLN0128 or +/- 4 hours for alisertib), then the dose should be skipped and considered a missed dose. Patients should record any missed

doses in their diary and resume drug administration at the next scheduled time with the prescribed dosage. Under no circumstance should a patient repeat a dose or double-up doses.

12.2 Definitions of Dose-Limiting Toxicity

Dose limiting toxicities are defined according to the AE profile observed during the first 28 days of study drug administration in the dose escalation portion of the study and as described below. All AEs should be considered possibly related to the study drug unless such relationship can be definitively excluded.

Toxicity will be evaluated according to NCI CTCAE Version 4.03 . A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to treatment with MLN0128 or alisertib:

- Grade 3 or higher nonhematologic toxicity, despite adequate treatment, except for the following:
  1. Grade 3 hyperglycemia lasting ≤ 72 hours (all patients should receive optimal antiglycemic treatment, including insulin, as clinically indicated).
  2. Grade 3 rash that resolves to ≤ Grade 1 within 3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary).
  3. Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all patients should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment).
  4. Grade 3 nausea, vomiting and/or diarrhea lasting ≤ 72 hours despite maximal supportive therapy.
- Grade 4 neutropenia lasting > 7 days in the absence of growth factor support.
- Grade 3 neutropenia of any duration accompanied by fever ≥ 38.5°C and/or systemic infection.
- Thrombocytopenia with clinically significant bleeding.
- Any other ≥ Grade 4 hematologic toxicity.
- Inability to administer at least 75% of planned doses of MLN0128 or alisertib within Cycle 1, due to study drug-related toxicity.
- Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk.

Patients who experience an AE that meets the definition of a DLT during or after completing Cycle 1 should have their study drug treatment interrupted. If the event resolves to Grade 1 or baseline values within 2 weeks of interrupting planned therapy, and in the opinion of the investigator the benefits of continuing treatment outweigh the risks posed by the toxicity, patients may continue study treatment with MLN0128 and alisertib with dose reduction of the agent responsible for toxicity.

12.3 MLN0128 Dose modification Guidelines

MLN0128 should be administered in continuous cycles, which should continue unless the patient has a Grade 3 or greater MLN0128 -related event. Guidelines for dose interruption and for dose reduction are as follows:

Criteria for Dose Interruption and Dose Modification During a Cycle
Administration of MLN0128 should be withheld for MLN0128 treatment-related toxicities that are Grade 3 or higher, despite supportive treatment per standard clinical practice.
The following nonhematologic toxicities attributed to MLN0128 would not require dose interruption:

- Grade 3 or higher nausea and/or emesis in the absence of optimal anti-emetic prophylaxis. (Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.)
- Grade 3 or higher diarrhea that occurs in the absence of optimal supportive therapy.

If the event resolves to Grade 1 or baseline values within 2 weeks of interrupting treatment, the patient may resume study treatment at a dose reduced by 1 level (see Table 1). Two dose reductions of MLN0128 will be allowed according to Table 1. If further dose reduction is required from 1 mg PO daily, then the dosing schedule can be modified to 5 days of treatment followed by 2 days rest without dosing. Dosing interruptions/delays of up to 14 days will be allowed for recovery from toxicities or inter-current illness. Longer interruptions can be considered if the patient is benefiting from therapy with MLN0128.Guidance for the management of common toxicities observed with MLN0128 hyperglycemia, hyperlipidemia, oral mucositis, rash, nausea/vomiting, and non-infectious pneumonitis are outlined in Section 12.8.

Table 2: Recommended Dose Interuptions and Dose Reductions for Toxicities Related to MLN0128 (except hyperglycemia, hyperlipidemia, oral mucositis, rash, nausea/vomiting and non-infectious pneumonitis)

Grade	MLN0128 Dose Interruption	MLN0128 Dose Modification
1-2	Treat on time	No change
3	Delay until ≤ Grade 1 or baseline	Reduce 1 dose level.
4	Delay until ≤ Grade 1 or baseline	Reduce 1 dose level. Permanent discontinuation can be considered at the treating Investigator's discretion.

12.4 Alisertib Dose Modifications Guidelines

Treatment with alisertib will be repeated every 21 days. In order for a new cycle of therapy to begin, the patient must meet the following criteria:

- ANC must be $\geq 1{,}500/mm^3$
- Platelet count must be $\geq 75{,}000/mm^3$.
- In addition, all toxicities considered by the investigator to be related to therapy with alisertib must have resolved to ≤ Grade 1 or to the patient's baseline values before a new cycle of therapy may begin.

If the patient fails to meet the above-cited criteria for retreatment, then initiation of the next cycle of therapy should be delayed for up to 1 week. At the end of that week, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should treatment need to be delayed for more than 1 week (ie, a rest period of more than 21 days) because of incomplete recovery from treatment-related toxicity, the dose of alisertib should be reduced by one dose level (Table 1) when therapy resumes. A second dose reduction may occur should treatment need to be delayed for more than 1 week because of incomplete recovery from treatment-related toxicity on the reduced dosage of alisertib. If further dose reduction is required from 20 mg PO BID, then the dosing schedule can be modified to 3 days of treatment followed by 4 days rest without dosing. Only 2 dose reductions of alisertib will be allowed according to Table 1. Dosing interuptions/delays of up to 14 days will be allowed for recovery from toxicities or inter-current illness. Longer interuptions can be considered if the patient is benefiting from therapy with alisertib. Growth factor support is permitted at the treating Investigator's discretion following delay or neutropenic fever, but should not be used prophylactically during Cycle 1.

12.4.1 Dose Modifications for Hematological Toxicity

If a patient experiences any of the following hematological toxicities during the dosing period, dosing with alisertib will be discontinued for the remainder of that cycle and the dose will be decreased 1 level for all subsequent cycles of treatment.

- Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting more than 7 consecutive days
- Grade 4 thrombocytopenia (platelet count < 25,000/µL) lasting more than 7 consecutive days
- Platelet count less than 10,000/µL at any time

- Grade 3 neutropenia with fever or infection, or both, where fever is defined as an oral temperature greater than 38.5°C

- Any thrombocytopenia with clinically significant bleeding

12.4.2 Dose Modifications for Non-Hematological Toxicities

If a patient experiences any of the following toxicities that are at least possibly related to alisertib during the dosing period, dosing will be discontinued for the remainder of that cycle and the dose will be decreased 1 level for all subsequent cycles of treatment, and treatment may resume after drug-related toxicities have resolved to ≤ Grade 1 or to baseline.

- Any Grade 3 nonhematological toxicity that is considered by the investigator to be related to alisertib other than:

    - Grade 3 or greater nausea or emesis, or both, that occurs in the absence of optimal antiemetic therapy (5-hydroxytryptamine 3 [5-HT3] serotonin receptor antagonist);

    - Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy with loperamide or a comparable anti-diarrheal;

- Grade 2 non-hematological toxicities that are considered by the investigator to be related to study drug and in the opinion of the investigator require dose reduction.

In general, study drug treatment should be discontinued if a patient experiences a Grade 4 toxicity. If, in the opinion of the investigator and study sponsor it is in the patient's interest to continue therapy with alisertib, then after recovery from the toxicity or toxicities in question to ≤ Grade 1 or to baseline values, the dose of alisertib should be reduced by at least 1 dose level with subsequent cycles of therapy.

When a dose reduction of alisertib is required, no re-escalation of dose will be permitted. If a patient requires more than 2 dose reductions, therapy with alisertib will be discontinued.

See also Section 12.8 Management of Clinical Events Related to MLN0128 and alisertib for management of oral mucositis, rash, and nausea/vomiting which may be overlapping toxicities related to both agents.

12.5 Excluded Concomitant Medications and Procedures and potential Drug-Drug interactions

The following medications and procedures are prohibited during the study:

- Other investigational agents including mTOR, PI3Kinase and AKT inhibitors
- Other anticancer therapies including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation or surgery (subjects can have palliative radiation or surgery in the study for pre-existing lesions)
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of MLN0128 related AE, ie, rash.
- Anti-epileptic drugs for subjects with treated brain metastasis
- Concomitant administration of any PPI is not permitted during the study. Patients receiving PPI therapy before enrollment must stop using the PPI for 7 days before their first dose of study drugs. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
- Consumption of grapefruit or grapefruit juice is not permitted during the study. Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study (See Appendix 4).
- Histamine-2 (H2) receptor antagonists are not permitted within 12 hours before and within 6 hours after MLN0128 or alisertib administration. Patients receiving histamine H2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H2 receptor antagonists include ranitidine, famotidine, nizatidine, and cimetidine.
- Neutralizing antacids and calcium preparations are not permitted within 2 hours before and 2 hours after MLN0128 or alisertib administration. Some anti-gas preparations may also have antacid properties, and should also not be permitted from 2 hours before until 2 hours after MLN0128 or alisertib administration.

12.6 Permitted Concomitant Medications and Procedures

Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose and subsequent doses of study drug, as needed throughout the study, and as clinically indicated per standard practice. When selecting an anti-emetic agent, drugs that do not have an effect on the QT interval, such as palonosetron, are preferred.

Histamine H2 receptor antagonists may be allowed, if needed provided that the histamine H2 receptor antagonist is not taken within 12 hours before and within 6 hours after study drug administration. Patients receiving histamine H2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H2 receptor antagonists include ranitidine, famotidine, nizatidine, and cimetidine.

Neutralizing antacid preparations (acid neutralizers) and calcium supplements may be taken as needed except from 2 hours before until 2 hours after MLN0128 or alisertib administration. Some anti-gas preparations may also have antacid properties, and should also not be permitted from 2 hours before until 2 hours after study drug administration.

Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9 should only be administered with caution, at the discretion of the investigator (see Appendix 4):

> CYP3A, 2C9, and 2C19 inducers: rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, primidone, St. John's Wort, bosentan, nafcillin, modafinil.
>
> CYP3A, 2C9, and 2C19 inhibitors: ketoconazole, itraconazole, voriconazole, posaconazole, boceprevir, telaprevir, fluconazole, clarithromycin, telithromycin, troleandomycin, erythromycin, nefazodone, mibefradil, conivaptan, diltiazem, verapamil, dronedarone, aprepitant, casopitant, tofisopam, ciprofloxacin, amiodarone, fluvoxamine, and ticlopidine.
>
> Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator.

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

Treatment with myeloid growth factors is permitted at the treating Investigator's discretion following delay or neutropenic fever, but should not be used prophylactically during Cycle 1.

12.7 Precautions and Restrictions

Patients who show evidence of hyperglycemia during the study should be encouraged to follow a low carbohydrate diet.

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

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

It is not known what effects MLN0128 or alisertib have on human pregnancy or development of the embryo or fetus. Therefore, women participating in this study should

avoid becoming pregnant, and men should avoid impregnating a female partner or donating sperm. Women of childbearing potential and men should use effective methods of contraception during and through 90 days after the last dose of study drug, as specified below.

Women must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form (ICF) through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- Practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
- Agree not to donate sperm during the course of this study or 120 days after receiving their last dose of study drug.

12.8 Management of Clinical Events Related to MLN0128 and Alisertib

12.8.1 Management of Hyperglycemia

In addition to obtaining fasting serum glucose (FSG) levels at clinic visits, all subjects will be given a glucometer to monitor their daily pre-dose fasting blood glucose (FBG) levels at home. Subjects will be instructed to notify the study staff immediately with any abnormal readings (ie, ≥ 150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no irregularities in the fasting blood glucose level are observed during a minimum of 6 consecutive months, then the frequency of in-home fasting glucose testing may be reduced to twice weekly if the investigator approves. Subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL and, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of fasting blood glucose levels will be reinstated to daily.

In the event that any FSG reading performed at the site indicates hyperglycemia (> upper limit of normal [ULN] or ≥ 110 mg/dL), the study staff should first ascertain that the subject was fasting at the time of the blood draw (ie, nothing by mouth for at least 8 hours prior to blood being obtained), had continued to take their concomitant antiglycemic medications should the subject have underlying diabetes mellitus, and repeat the FSG as needed. If the repeat FSG continues to demonstrate hyperglycemia, investigators should initiate steps to aggressively manage the hyperglycemia per standard clinical practice. The following guidelines are provided to aid the investigator in initiating antiglycemic therapies.

Based on the clinical experience from MLN0128 trials, most episodes of hyperglycemia observed have been Grade 1 or 2 that have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since instituting a standard regimen for early treatment of hyperglycemia. All subjects developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of subjects who develop Grade 1 hyperglycemia (FSG > ULN ≤ 160 mg/dL) or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as metformin. All subjects with Grade ≥ 2 hyperglycemia (FSG > 160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated while continuing on MLN0128. The investigator should consult an endocrinologist if needed to aid in optimizing the subject's hyperglycemia treatment plan.

It is recommended that subjects be treated initially with a fast acting, insulin sensitizer, such as metformin at 500 mg PO QD, and titrate up to a maximum of 1000 mg PO BID as needed. Concurrent addition to metformin of DPP-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution due to the higher risk of inducing hypoglycemia in subjects. The dose of oral hypoglycemic agents should be adjusted in subjects with renal insufficiency. In addition, patients should also be encouraged to follow a low carbohydrate diet once hyperglycemia is first observed.

Guidance on study drug dose modification for patients with hyperglycemia is provided in the following table

Table 3 Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
1	Fasting blood sugar >ULN to 160 mg/dL	• Continue close monitoring of blood sugar. • Initiate oral hypoglycemic agent.	None
2	>160 to 250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥3	>250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin.	Hold MLN0128 until ≤Grade 1. Resume MLN0128 based on timing of recovery after maximal treatment:

Table 3 Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
			• ≤1 week: resume MLN0128 at same dose and schedule. • >1 but ≤2 weeks: reduce MLN0128 by 1 dose level • >3 weeks: permanently discontinue MLN0128
Prevention/Prophylaxis: • Follow fasting glucose levels during clinic visits. • Monitor home glucometer test results. • Check HbA1c levels every 3 months during therapy. • Most episodes of Grade 1 or 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy at the lowest therapeutic dose is recommended to prevent higher grade hyperglycemia. • Fasting blood glucose levels ≥150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.			

HbA1c=glycosylated hemoglobin, ULN=upper limit of normal.

12.8.2 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided below

Table 4 Management of Hyperlipidemia

Grade	Description	Treatment	Dose Modification
1	Cholesterol >ULN to 300 mg/dL Triglycerides >150 to 300 mg/dL	None	None
2	Cholesterol >300 to 400 mg/dL Triglycerides >300 to 500 mg/dL	• Treat hyperlipidemia according to standard guidelines. • Triglycerides ≥500 mg/dL should be treated urgently, due to risk of pancreatitis.	• Maintain dose, if tolerable. • If toxicity becomes intolerable, interrupt MLN0128 until recovery to ≤Grade 1. Re-initiate MLN0128 at the same dose level
3	Cholesterol >400 to 500 mg/dL Triglycerides >500 to 1000 mg/dL	Same as for Grade 2.	Hold MLN0128 until recovery to ≤Grade 1, then reinitiate MLN0128 at a dose reduced by 1 level
4	Cholesterol >500 mg/dL Triglycerides >1000 mg/dL	Same as for Grade 2.	Same as for Grade 3.

Prevention/Prophylaxis:

Life-style modifications, as appropriate (balanced diet, limit alcohol consumption, increase physical activity)

ULN=upper limit of normal.

12.8.3 Management of Oral Mucositis

Guidance on study drug dose modification for patients with oral mucositis

Table 6 Management of Oral Mucositis

Grade	Description	Treatment	Dose Modification
1	Asymptomatic or mild symptoms.	• Nonalcoholic mouth wash, or 0.9% salt water rinse. • Consider topical corticosteroids at earliest signs of mucositis.	None
2	Moderate pain, not interfering with oral intake. Modified diet indicated.	• Topical analgesic mouth treatments. • Topical corticosteroids. • Initiate antiviral or antifungal therapy, if indicated.	• Maintain alisertib and MLN0128 dose if tolerable • Hold alisertib* and MLN0128 if intolerable until recovery to ≤Grade 1, then restart at same dose.
3	Severe pain, interfering with oral intake.	• Same as for Grade 2. • Consider intralesional corticosteroids.	• Hold alisertib* and MLN0128 until recovery to ≤Grade 1, then restart alisertib* and MLN0128 at a dose reduced by 1 level
4	Life-threatening consequences.	• Same as for Grade 2 • Consider intra-lesional corticosteroids	• Stop alisertib* and MLN0128

Prevention/Prophylaxis:

- Initiation of a nonalcoholic mouth wash, or 0.9% salt water rinses 4 to 6 times daily is strongly recommended at the start of therapy before signs of mucositis develop.
- Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis, as they may worsen mouth ulcers.

***Only if oral mucositis developed during alisertib treatment or is felt to be at least possibly related to alisertib treatment**

12.8.4 Management of Rash

Guidance on study drug dose modification for patients with rash is provided below

Table 7 Management of Rash

Grade	Description	Treatment	Dose Modification
≤2	Macules/papules covering ≤30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment and/or oral anti-histamines or antibiotics.	None
≥3	Macules/papules covering >30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment, oral anti-histamines, oral antibiotics, and/or pulsed steroids.	Hold alisertib* and MLN0128 until ≤Grade 1 Resume alisertib* and MLN0128 based on timing of recovery to ≤Grade 2: • ≤3 weeks: reduce alisertib and MLN0128 by 1 dose level • >3 weeks: stop alisertib and MLN0128 and discontinue patient from the study

Prevention/Prophylaxis:

- Rash should be managed aggressively. The investigator should consider consulting a dermatologist or other specialist, if needed.
- A skin biopsy at the site of rash should be considered as soon as possible after the initial episode.

***Only if rash developed during alisertib treatment or is felt to be at least possibly related to alisertib treatment**

12.8.5 Management of Nausea/Vomiting

Guidance for patients with nausea and/or vomiting is provided in the table below

Table 8 Management of Nausea/Vomiting

Grade	Description	Treatment	Dose Modification
≤2	Loss of appetite with or without decreased oral intake; 1 to 5 episodes of vomiting within 24 hours.	• Maximize anti-emetic therapy. • Consider IV fluid hydration.	None
≥3	Inadequate oral intake; ≥6 episodes of vomiting within 24 hours.	• Maximize anti-emetic therapy. • Initiate tube feeding, IVF or TPN.	Hold alisertib* and MLN0128 until ≤ Grade 1, then resume treatment without dose modification

Prevention/Prophylaxis:

Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications are encouraged and may be used before each MLN0128 dosing as needed throughout the study. Because of the potential of benzodiazepines

to cause sedation, the use of benzodiazepines for antiemetic prophylaxis should be reserved for patients who cannot be satisfactorily managed otherwise.

IV=intravenous, IVF=intravenous fluids, TPN=total parental nutrition.

***Only if nausea/vomiting developed during alisertib treatment or is felt to be at least possibly related to alisertib treatment**

12.8.6 Management of Cardiac Abnormalities

Management of Patients With Possible Cardiac Instability

For patients showing signs of cardiac instability after MLN0128 administration, additional monitoring onsite before clinic discharge should be considered.

Management of Patients With Left Ventricular Dysfunction

Guidance for MLN0128 dose adjustment for patients with left ventricular dysfunction is provided below.

Table 9 Management of Left Ventricular Dysfunction

Grade	Description	Dose Modification
1	Asymptomatic decline in: LVEF >15% from baseline values, OR LVEF >10% to 15% from baseline values and is below institution's LLN.	No change; continue MLN0128 at the same dose and schedule
≥2	Symptomatic cardiac dysfunction/congestive heart failure.	Discontinue treatment.

LLN=lower limit of normal, LVEF=left ventricular ejection fraction.

Management of Patients with QTc Prolongation

Guidance for MLN0128 dose adjustment for patients exhibiting a prolonged QTc interval is provided below.

Table 10 Management of QTc Prolongation

Grade	Description	Treatment	Dose Modification
2	480 msec <QTc <501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication, etc).	None; continue MLN0128 at the same dose and schedule.

Table 10 Management of QTc Prolongation

Grade	Description	Treatment	Dose Modification
≥3	QTc ≥501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication).(a) Consider a formal consult by a cardiologist; Notify the study doctor; Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.	Hold MLN0128 The decision whether to reinitiate MLN0128 with or without dose reduction and additional monitoring in those patients who had asymptomatic prolonged QTc ≥501 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated MLN0128, and appear to have benefitted from treatment with either disease control or response, will be agreed to by the investigator and the study doctor on a case-by-case basis.

ECG=electrocardiogram, IV=intravenous, msec=milliseconds, QTc=QT interval corrected for heart rate.
(a) A list of medications known to prolong QTc can be found at https://www.crediblemeds.org/new-drug-list/

12.8.7 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness and Fatigue)

Guidance on dose adjustment for patients with other nonhematologic toxicities is provided below

Table 11 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Initiate appropriate medical therapy and monitor.	If tolerable, then no adjustment is required.
2	Moderate; minimal, local or noninvasive intervention indicated.	Initiate appropriate medical therapy and monitor.	• If tolerable, no adjustment required. • If toxicity becomes intolerable, hold MLN0128 until recovery to ≤Grade 1, then reinitiate at same dose.

Table 11 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
≥ 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated		Hold MLN0128 until recovery to ≤ Grade 1. Reinitiate MLN0128 at dose reduced by 1 level.

If asthenia, weakness or fatigue occurs during alisertib dosing or is considered to be at least possibly related to alisertib treatment, then see Section 12.4.2 Dose Modifications for Non-Hematologic Toxicities for alisertib dose modifications.

12.8.8 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

Guidance on dose adjustment for patients with AST/ALT elevations is provided below

Table 12 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

Grade	Description	Treatment	Dose Modification
1	>ULN to 3×ULN	None	None
2	Asymptomatic with levels 3 to 5×ULN; >3×ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.	• Closely monitor LFTs at least weekly or more frequently as indicated. • Assess patient for other causes of transaminitis (eg, past medical history, concomitant medications).	None
3	>5 to 20×ULN; >5×ULN for >2 weeks	Same as for Grade 2.	Hold MLN0128 until ≤Grade 1; Restart MLN0128 at the same dose;
4	>20×ULN	Same as for Grade 2.	Stop MLN0128 and discontinue patient from the study.
Prevention/Prophylaxis: Ensure proper screening of patients for study participation.			

LFTs=liver function tests, ULN=upper limit of normal.

12.8.9 Management of Non-infectious Pneumonitis

Guidance for the management of pneumonitis is provided below

Table 13 Management of Non-infectious Pneumonitis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic: Radiographic findings only.	Rule out infection and closely monitor.	None
2	Symptomatic: Not interfering with activities of daily living.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Interrupt MLN0128 • When symptoms ≤Grade 1, reinitiate MLN0128 at a dose reduced by 1 level. If no recovery within 4 weeks, then discontinue MLN0128.
3	Symptomatic: Interfering with activities of daily living; Requires administration of oxygen.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Interrupt MLN0128 until symptoms resolve to ≤Grade 1. • Consider reinitiating MLN0128 at a dose reduced by 1 level . • If toxicity recurs at Grade 3, discontinue MLN0128.
4	Life-threatening: Ventilatory support indicated.	Rule out infection and consider treatment with corticosteroids.	Discontinue MLN0128.

12.9 Management of Clinical Events Related to alisertib

12.9.1 Management of Central Nervous System Effects

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

If the patient's level of consciousness is considered to be life-threatening, necessary measures should be instituted to secure the airway, ventilation, and intravenous access. Flumazenil (Romazicon®) is a selective benzodiazepine receptor antagonist that is intended as an adjunct to, not as a substitute for, the proper management of benzodiazepine overdose. Although there is neither preclinical nor clinical experience with flumazenil and alisertib, the use of flumazenil should be considered if the level of alisertib-associated sedation is considered to be life-threatening. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. Continued monitoring is particularly important in the

case of alisertib given its half-life and the comparatively brief half-life of flumazenil in the CNS (20-30 minutes). Flumazenil should be administered according to its label.

12.10 Description of Investigational Agents

12.10.1 MLN0128

MLN0128 will be supplied as capsules for oral administration. The study drug is available in 3 dose strengths, 1 mg, 3 mg, and 5 mg, each containing 1 mg, 3 mg, and 5 mg of MLN0128, respectively, in addition to the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant), and hard gelatin capsule. All 3 dose strengths are formulated into size 2 capsules, and each dose strength is differentiated by color, as listed below:

- MLN0128 capsules, 1 mg - white opaque color
- MLN0128 capsules, 3 mg – orange opaque color; and/or
- MLN0128 capsules, 5 mg – grey opaque color

12.10.2 Alisertib

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

12.11 Preparation, Reconstitution, and Dispensation

12.11.1 MLN0128

MLN0128 study drug will be provided in labeled bottlesd in accordance with all applicable regulations. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN0128 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 capsules.

12.11.2 Alisertib

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

Alisertib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling alisertib. It is recommended that gloves and protective garments be worn during preparation.

12.12 Packaging and Labeling

12.12.1 MLN0128

MLN0128 will be provided by Millennium and will be handled at the investigative site as open-label material. Sites must store according to the labeled conditions.
MLN0128 capsules are packaged in HDPE bottles with polypropylene, child-resistant caps and induction seal. For all dose strengths, each bottle contains 30/60 capsules.

12.12.2 Alisertib

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

As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the Study Manual.

12.13 Storage, Handling, and Accountability

12.13.1 MLN0128

Upon receipt at the investigative site, drug should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F to 86°F). All temperature excursions will be reported for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All drug supplies should be used before the retest expiry date. Because MLN0128 is an investigational agents, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), the skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.
Patients will receive instructions for home storage and administration of MLN0128.
.
Accountability for MLN0128 at all study sites is the responsibility of the sponsor-investigator.

12.13.2 Alisertib

Tablets should remain in the bottle provided until use. The container should be stored at the investigative site at controlled room temperature (20-25°C; 68-77°F; excursions are permitted from 15-30°C; 59-86°F) and used before the retest expiry date provided by Millennium. Containers should be kept closed during storage.

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

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

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

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

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

12.14 Study Compliance

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

12.15 Treatment Assignment

Treatment in the dose escalation cohort will be assigned based on the dose escalation scheme of the study as described in Section 10. Once the dose escalation portion of the study is complete, enrollment to the dose expansion cohorts will begin.

12.16 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation

- Lost to follow-up
- Progressive disease
- Study terminated
- Other

Patients withdrawn from the study in the dose escalation cohort during cycle 1 will be replaced unless they are withdrawn due to an adverse event. Patients enrolled in the dose expansion cohort who withdraw prior to completing the correlative studies will be replaced.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

13. STATISTICAL AND QUANTITATIVE ANALYSES

13.1 Statistical Methods

Primary Objective:

The MTD will be defined as the highest dose level evaluated in which 0 or 1 patient out of 6 patients experiences DLT.

Secondary Objectives:

1. Safety: Adverse events will be tabulated by type and grade.

2. Pharmacokinetics: The AUC and Cmax will be determined for MLN0128 and MLN8237. The distribution of these parameters for MLN0128 when administered with MLN8237 and for MLN8237 when administered with MLN0128 will be compared to the appropriate single agent administration control data.

3. Translational Endpoints: All analyses with respect to the translational component of this study are intended to be hypothesis-generating and descriptive in manner. Biologic correlates will be obtained from tumor biopsies as outlined above. Baseline levels of these markers will be correlated with clinical outcome (i.e. response, time to progression, and adverse events) using regression methods (Cox model for tie to event, logistic regression for binary outcome, Poisson regression for counts). Additionally, the dynamic change in markers will be assessed from baseline to Cycle 1 Day 7 and Cycle 2 Day 7 in both Expansion Cohort Groups using repeated measures/mixed models analysis. For the functional imaging performed in select patients in the Dose Expansion Groups, FDG-PET images will be analyzed with AsiProVM and mean change in SUV will be compared to baseline. For DCE-MRI analysis, the AUC for the gadolinium versus time curve and the initial AUC will be calculated using the trapezoidal rule in Microsoft Excel. Data will be

fitted to a two-compartment model to estimate K_{trans} and K_{ep} which will be compared to baseline.

4. Efficacy: Analysis of efficacy measures will be descriptive. The best overall response will be summarized using the number and percent of patients in each tumor response category along with the two-sided exact binomial 95% confidence intervals. Time to progression will be defined as the time from the first day of treatment to the first observation of disease progression. If a patient dies without documentation of disease progression, the patient will be considered to have had tumor progression at the time of their death unless there is sufficient documented evidence to conclude no progression occurred prior to death. The distribution of disease-free survival will be estimated using the method of Kaplan and Meier. The median time and its 95% confidence interval will be reported.

13.1.1 Determination of Sample Size

The total number of patients enrolled in the Dose Escalation Cohort will depend on the number of dose cohorts required to identify the MTD. Design considerations were not made with regard to explicit power and type I error considerations, but to obtain preliminary safety , PK, and efficacy information in this patient population. Escalation to the next dose cohort will depend on the probability of DLT at a given dose. When 1 of 3 patients develops a DLT and the cohort is expanded to 6 patients, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of < 10%.

A maximum of 6 patients can be enrolled at each dose level. With 6 potential dose levels and an Expansion Cohort of 30 patients with TNBC, the maximum number of patients that can be enrolled is 56 and the minimum number is 6.

The total planned enrollment in the expansion study is up to approximately 30 patients in three cohort groups. This sample size will provide a reasonable chance (> 75%) of observing at least one or more adverse events when the true frequency of the adverse event is between 10%−15% at the given dose level. Specifically, for a given adverse event with a true rate of 15%, 10%, 5%, or 1%, the probability of observing at least one such adverse event in the combined cohort of 20 patients is 99%, 86%, 64%, or 18%, respectively In addition, assessment of the response rate in 20 patients will exclude with 95% confidence, a true response rate of 15% or higher if no response is observed.

13.1.2 Randomization and Stratification

Randomization and stratification will not be used in this trial.

13.1.3 Populations for Analysis

Safety, PK and efficacy analysis will be based on patient data collected through study discontinuation. The analyses will all be based on all patients receiving at least 1 dose of study drug.

13.1.4 Procedures for Handling Missing, Unused, and Spurious Data

Missing values will not be estimated or imputed given the small sample size. All available data will be included in data listings. Repeated measures analyses of dynamic changes in biomarkers will use maximum likelihood methods which are robust to data being missing at random.

Sensitivity analyses will be used to assess impact on spurious observations on statistical summaries.

13.1.5 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized by dose level. No formal statistical analysis will be performed on these data.

13.1.6 Efficacy Analysis

Best overall response rate will be computed with an exact 95% Binomial confidence interval for each tumor response category. Progression free survival will also be analyzed using Kaplan Meier methods including 95% confidence interval for median PFS.

Efficacy will be performed using all the patients who received at least one cycle of study drug or were withdrawn during cycle 1 for progression.

13.1.7 Pharmacokinetics

Pharmacokinetic parameters will be derived from the blood PK samples and will be analyzed using descriptive statistics, including the median, mean and 95% confidence intervals around parameter estimates by dose level and time point. PK analyses will be conducted on all patients that received at least one dose of the drug and provide at least one post-treatment sample.

13.1.8 Safety Analysis

The safety evaluation will be based on all patients that received at least one dose of the drug and will include AEs, SAEs, and changes from baseline in laboratory evaluations, vital signs, and physical examinations. Summaries will be provided overall and by does group. The number and percentage of subjects reporting treatment-emergent AEs (TEAE) will be summarized overall and by the worst CTCAE grade, with a breakdown by dose . Similarly, the number and percentage of subjects reporting TEAEs considered related to each study drug will be summarized.

14. ADVERSE EVENTS

14.1 Definitions

14.1.1 Adverse Event Definition

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

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

14.1.2 Serious Adverse Event Definition

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

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

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

14.2 Procedures for Reporting Serious Adverse Events

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. 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 one comprehensive event.

Adverse Events which are serious must be reported to Millennium Pharmacovigilance (or designee) from the time of consent up to and including 30 days after administration of the last dost of MLN0128 or alisertib. Any SAE that occurs at any time after completion of MLN0128 treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). 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).

Since this is an investigator-initiated study, the sponsor-investigator Jennifer R. Diamond, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB. Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance or designee:

- **Fatal and Life Threatening SAEs:** within 24 hours of the sponsor-investigator's observation or awareness of the event
- **All other serious (non-fatal/non life threatening) events:** within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The Sponsor will send all SAE reports to Millennium Pharmacovigilance (or designee) within 24 hours but no later than 4 calendar days as per any agreements.

The SAE report must include at minimum:

- **Event term(s)**

- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to MLN0128 and alisertib administration.

Follow-up information on the SAE may be requested by Millennium Pharmacovigilance (or designee).

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

US and Canada
Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)
Fax #: 1 202 315 3560
E-mail: takedaoncocases@cognizant.com

Suggested Reporting Form:

- SAE Report Form (a sample will be provided)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

14.3 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-investigator must fax a completed Pregnancy Form to the Millennium Pharmacovigilance or designee immediately (see Section 12.2). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and

Millennium Pharmacovigilance or designee will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Pharmacovigilance or designee (see Section 12.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

Pregnancy Report Form (a sample will be provided)

15. ADMINISTRATIVE REQUIREMENTS

15.1 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 Millennium (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, call 1-844-ONC-TKDA (1/844-662-8532) email: GlobalOncologyMedinfo@takeda.com

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 12.2).

16. DATA AND SAFETY MONITORING

The Sponsor Investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues

- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the Investigators and Clinical Research Coordinators (CRCs) at weekly disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The Sponsor Investigator will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six month report by the DSMC will then need to be submitted by the site to the IRB of record at the time of continuing review.

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18. APPENDICES

Appendix 1: Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

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

Source: Oken MM, 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.(36)

Appendix 2: Cockcroft-Gault Equation

For men:

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

OR

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

For women:

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

OR

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

- Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41 (37).

Appendix 3: New York Heart Association Classification of Cardiac Disease

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

- Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.(38)

Appendix 4: List of Relevant Cytochrome P450 Inhibitors and Inducers

Strong CYP2C19 Inhibitors		
fluconazole	fluvoxamine	ticlopidine
Moderate CYP3A4 Inhibitors		
amprenavir	darunavir/ritonavir	fosamprenavir
aprepitant	diltiazem	grapefruit juice (a)
atazanavir	erythromycin	imatinib
ciprofloxacin	fluconazole	verapamil
Strong CYP3A4 Inhibitors		
boceprevir	ketoconazole	ritonavir
clarithromycin	lopinavir/ritonavir	saquinavir
conivaptan	mibefradil (b)	telaprevir
grapefruit juice (a)	nefazodone	telithromycin
indinavir	nelfinavir	voriconazole
itraconazole	posaconazole	
Clinically Significant Enzyme Inducers		
carbamazepine	rifabutin	St. Johns Wort
phenobarbital	rifampin	
phenytoin	rifapentine	

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Note that these lists are not exhaustive.

(a) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

(b) Withdrawn from the United States market because of safety reasons.