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

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

- Named persons or organizations associated with the study.

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

PROTOCOL

An Umbrella Study to Evaluate MLN1117 in Combination with Taxanes (Docetaxel or Paclitaxel) and Other Investigational Anticancer Agents for the Treatment of Patients with Previously Treated Advanced and Metastatic Gastric and Gastroesophageal Adenocarcinoma

MLN1117 in Combination with Docetaxel, Paclitaxel, and Other Investigational Anticancer Agents to Treat Patients with Gastric and Gastroesophageal Adenocarcinoma

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "Sponsor", or "Takeda"
Study Number:	C032-6001 (also known as MLN1117-1003)
IND Number:	112,048 **EudraCT Number:** 2015-001032-38
Compound:	MLN1117 (also known as TAK-117)

Original Protocol Date:	24 June 2015
Amendment 1 Date:	11 December 2015
Amendment 2 Date:	25 January 2016

[redacted]

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 11.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America	Europe
Serious adverse event and pregnancy reporting	See Section 11.0	See Section 11.0

[redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD _____ Date
MD, PhD, Oncology Clinical Research, PPD

PPD _____ Date
PhD, Oncology Statistics, PPD

PPD _____ Date
MD, PhD, Oncology Clinical Research, PPD

PPD _____ Date
PhD, Clinical Pharmacology, PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 11.1.3 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

[redacted]

1.3 Protocol Amendment 2 Summary of Changes

This document describes the changes in reference to Protocol Incorporating Amendment No. 2.

The primary purpose of this amendment is to revise the definition of dose-limiting toxicity (DLT) in regards to the attribution of study drug causality, and to remove inaccurate exceptions for Grade 4 nonhematologic treatment-emergent adverse events (TEAEs).

In addition, a minor change was made to the window for obtaining pretreatment tumor biopsies in Part 2 of the study. Grammatical and editorial changes have also been made for purposes of clarification and correction of inconsistencies. Full details on changes to the text are given in Appendix H. The following is a summary of the changes.

1. The DLT definition has been clarified to state that the listed events will qualify as DLTs when they are considered at least possibly related to 1 or both of the study drugs (MLN1117, TAK-659, alisertib, paclitaxel, or docetaxel) administered in a given combination regimen.

   Justification: To ensure that the DLT assessments reflect the toxicity of the administered combination regimens and not exclusively a single agent within the combination.

2. The DLT-qualifying event list has been updated to reflect that a Grade 4 TEAE of diarrhea and/or vomiting will be considered a DLT regardless of the event duration and/or response to supportive care treatment.

   Justification: Grade 4 events are life-threatening per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 and, therefore, are always DLTs.

3. For Part 2 of the study, the required timeframe during which fresh pretreatment tumor biopsies may be obtained has been expanded. If a fresh biopsy is needed, it may be obtained at any time within the 28-day screening window.

   Justification: To allow for flexibility in obtaining fresh pretreatment biopsies.

4. Minor edits have been made regarding archival tumor specimens and tumor biopsy samples.

   Justification: To provide clarification.

5. Typographical errors, punctuation, grammar, and formatting have been corrected.

TABLE OF CONTENTS

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[redacted]

LIST OF IN-TEXT TABLES

[redacted]

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

[redacted]

2.0 STUDY SUMMARY

<table>
<tr><td>Name of Sponsor(s):
Millennium Pharmaceuticals, Inc.</td><td colspan="2">Compounds:
MLN1117 (TAK-117), TAK-659, MLN8237 (alisertib)</td></tr>
<tr><td>Title of Protocol: An Umbrella Study to Evaluate MLN1117 in Combination with Taxanes (Docetaxel or Paclitaxel) and Other Investigational Anticancer Agents for the Treatment of Patients with Previously Treated Advanced and Metastatic Gastric and Gastroesophageal Adenocarcinoma</td><td>IND No.: 112,048</td><td>EudraCT No.:
2015-001032-38</td></tr>
<tr><td>Study Number: C032-6001 (also known as MLN1117-1003)</td><td colspan="2">Phase: 1b</td></tr>
<tr><td colspan="3">Study Design:
This is an open-label, multicenter, phase 1b study of MLN1117 (also known as TAK-117) in combination with TAK-659, alisertib (MLN8237), paclitaxel, or docetaxel in adult patients with locally advanced and metastatic gastric or gastroesophageal adenocarcinoma. The study consists of a dose escalation phase in patients with solid tumors (Part 1) and a dose expansion phase in patients with gastric or gastroesophageal junction cancers (Part 2). The statistical design for the dose expansion consists of equal randomization and adaptive randomization phases.
Part 1 (Dose Escalation)
During Part 1, the dose of MLN1117 will be escalated (planned doses of 300 mg, 600 mg, and 900 mg) according to a 3+3 dose escalation scheme (Section 9.3), while TAK-659, alisertib, paclitaxel, and docetaxel will be administered at a fixed dose and regimen until the maximum tolerated dose (MTD) or recommended dose for Part 2 is determined. Serial pharmacokinetic (PK) samples will be collected at prespecified time points in Cycle 1 to characterize the PK of MLN1117 when given in each of the combination regimens, and the PK of alisertib and TAK-659 when given in combination with MLN1117. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 [1].
Part 2 (Dose Expansion)
All patients who enter Part 2 of the study will be screened to determine whether or not their tumor tissue is positive for Epstein-Barr virus (EBV) (approximately 9% of patients with gastric cancer) [2]. An estimated 28 patients who are EBV positive will be assigned to treatment with TAK-659 in combination with MLN1117 (Cohort A). Patients who are EBV negative, initially will be randomized equally to 1 of the other treatment cohorts, 5 patients per group: MLN1117+alisertib (Cohort B), MLN1117+paclitaxel (Cohort C), or MLN1117+docetaxel (Cohort D). These patients will be assessed using a proportional weighted clinical utility function (allocating specific weights for complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]). Disease response will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [3]. Patients then will be randomized to treatment according to an adaptive randomization algorithm, which incorporates weighted clinical utility function. The resulting probability will be updated continually per accumulating data on the associations between the overall response rate (ORR) and Bayesian stopping rules. Adaptive randomization will be applied to newly enrolling patients every 2 months based on cumulative data. The adaptive randomization will increase the opportunity for each patient to receive the most effective experimental treatment possible based on posterior probabilities.
ORR will be used as the efficacy benchmark: target 25% (0.25); undesirable 10% (0.1). Early stopping rules will be prespecified if there is a clear signal of efficacy or lack of efficacy. The stopping rules are as follows: (1) achieve maximum sample size of each arm (30 patients); (2) stop an arm if probability (Pr) (response rate [RR]>0.25/Data) >80% and Pr (RR>0.10)/Data) >90%; (3) suspend accrual to an arm if Pr (RR≤0.10/Data) >80%. The treatment arm(s) is/are chosen in relation to the efficacy bar prespecified (target and undesirable); therefore, it is possible to select multiple treatment arms per this study design.</td></tr>
</table>

[redacted]

Adverse events (AEs) will be assessed, and laboratory values, vital signs measurements, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of MLN1117 when administered in combination with TAK-659, alisertib, paclitaxel, or docetaxel.

Sparse PK blood samples will be collected at prespecified time points for all patients in all treatment cohorts to contribute to future population PK analysis of MLN1117, TAK-659, and alisertib.

Primary Objectives:

The primary objective in Part 1 (dose escalation) is:

- To determine the initial safety of MLN1117 when administered with each of the combination partners measured as the MTD or recommended Part 2 dose.

The primary objective in Part 2 (dose expansion) is:

- To evaluate the ORR as the primary efficacy measure of MLN1117 in combination with each of the combination partners in patients with gastric or gastroesophageal junction adenocarcinoma.

Secondary Objectives:

The secondary objective in Part 1 (dose escalation) is:

- To evaluate initial activity for each combination.

The secondary objective in Part 2 (dose expansion) is:

- To evaluate additional efficacy measures, such as progression-free survival (PFS), disease control rate, duration of response (DOR), time to progression (TTP), and overall survival (OS) of MLN1117 in combination with each of the combination partners in patients with gastric or gastroesophageal junction adenocarcinoma.

The secondary objectives in Parts 1 and 2 are:

- To determine the recommended phase 2 dose (RP2D).
- To evaluate the overall safety and tolerability of MLN1117 in combination with each of the combination partners.
- To evaluate the PK of MLN1117 when dosed in combination with alisertib, TAK-659, docetaxel, or paclitaxel, and to evaluate the PK of alisertib and TAK-659 when these agents are dosed in combination with MLN1117.

Subject Population: Male and female patients aged 18 years or older with advanced solid tumor with no other standard therapeutic option (Part 1 only). In Part 2, patients with stage IIIB or IV gastric or gastroesophageal junction adenocarcinoma progressing to a previous first line of systemic therapy for advanced or metastatic disease.

Number of Subjects:	**Number of Sites:**
Part 1 (dose escalation): Estimated 60 patients; 15 patients in each combination treatment group, with potentially 3 to 6 patients in each dose cohort. Part 2 (dose expansion): Estimated maximum of 118 patients Cohort A (MLN1117+TAK-659): estimated 28 patients Cohort B (MLN1117+alisertib): estimated 30 patients Cohort C (MLN1117+paclitaxel): estimated 30 patients Cohort D (MLN1117+docetaxel): estimated 30 patients Estimated total: 149 to 178 patients (based on adaptive randomization and rules specified to achieve efficacy bar; treatment arm[s] may be selected early without achieving target sample size of 30).	Approximately 30 sites in North America and Europe.

[redacted]

Dose Level(s):	**Route of Administration:**
Cohort A: Starting dose for MLN1117, 300 mg orally (PO) once daily (QD) for 3 days on (Days 1-3, 8-10, 15-17, and 22-24) and 4 days off per week in each 28-day cycle. TAK-659 100 mg PO, continuous QD dosing in each 28-day cycle. **Cohort B**: Starting dose for MLN1117, 300 mg PO QD for 3 days on (Days 1-3, 8-10, 15-17, and 22-24) and 4 days off per week in each 28-day cycle. Alisertib 40 mg PO twice daily (BID) for 3 days on (Days 1-3, 8 10, and 15-17) and 4 days off per week in Weeks 1-3, and 1 week off in each 28-day cycle. **Cohort C**: Starting dose for MLN1117, 300 mg PO QD for 3 days on (first weekly dose on the day after paclitaxel each week; Days 2-4, 9-11, 16-18, and 23-25) and 4 days off per week in each 28-day cycle. Paclitaxel, 80 mg/m^2 intravenously (IV) once weekly on Days 1, 8, and 15, and 1 week off, in each 28-day cycle. **Cohort D**: Starting dose for MLN1117, 300 mg PO QD for 3 days on (first dose on the day after docetaxel; Days 2-4, 9-11, and 16-18) and 4 days off per week in each 21-day cycle. Docetaxel, 75 mg/m^2 IV on Day 1 once every 3 weeks in a 21-day cycle.	MLN1117, oral TAK-659, oral Alisertib, oral Paclitaxel, intravenous Docetaxel, intravenous
Duration of Treatment:	**Period of Evaluation:**
Patients may receive study drugs until they experience PD or unacceptable toxicity. The maximum duration of treatment for patients will be 1 year for MLN1117, alisertib, and TAK-659, and 6 cycles for paclitaxel and docetaxel. If it is necessary to discontinue paclitaxel or docetaxel due to cumulative toxicity, it is possible to continue treatment with MLN1117 as single agent. Patients with clinical benefit can receive MLN1117, alisertib, or TAK-659 beyond 1 year. If it is necessary to discontinue MLN1117 for safety reasons, the patient should be withdrawn from the trial. For special circumstances, in which it is recommended that the patient continue only on the companion drug, agreement between the investigator and sponsor is required. Paclitaxel and docetaxel may be administered after Cycle 6 if the investigator and sponsor determine that the patient would derive benefit from continued treatment.	Patients will be followed for 30 days after the last dose of any study drug, or the start of subsequent alternative anticancer therapy to permit the detection of any delayed treatment-related AEs. Patients who discontinue study drug treatment for reasons other than PD will undergo computed tomography/magnetic resonance imaging (CT/MRI) scans every 12 weeks from End of Treatment (EOT) until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the discontinuation of study treatment, whichever occurs first. Patients will be followed for OS every 12 weeks until death or until 1 year after the last dose of study drug, whichever occurs first.
Main Criteria for Inclusion:	
Male and female patients aged 18 years or older at the time of consent. In Part 1 (dose escalation), patients must have a histologically confirmed diagnosis of advanced solid tumor, including but not limited to gastric or gastroesophageal adenocarcinoma, and are refractory to or relapsed after prior line(s) of therapy with no effective therapeutic options available. In Part 2 (dose expansion), patients must have a histologically confirmed diagnosis of metastatic or locally advanced adenocarcinoma of the stomach or gastroesophageal junction (Stage IIIb or IV according to International Union Against Cancer [UICC] tumor, node, metastases [TNM] classification, 7th edition), with at least 1 measurable lesion per RECIST, Version 1.1 by radiographic techniques (CT or MRI), and have received 1 prior systemic chemotherapy regimen for advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction with	

documented PD.

Main Criteria for Exclusion:

Patients who have received prior systemic anticancer therapies, or other investigational agents or radiotherapy within 2 weeks before first dose of study drug; are receiving treatment with P-glycoprotein (P-gp) inhibitors/inducers (MLN1117+TAK-659 arm only); have received strong cytochrome P-450 (CYP) 3A4 inducers/inhibitors or proton pump inhibitors (PPIs) within 7 days before the first administration of study drug or have conditions that require the concomitant use of CYP3A4 inducers/inhibitors or PPIs during the course of the study; have poorly controlled diabetes mellitus; have signs of peripheral neuropathy ≥NCI CTCAE Grade 2; have symptomatic brain metastases or brain metastases with a stable neurologic status for <2 weeks after completion of the definitive therapy and steroids. In Part 2 (dose expansion), prior treatment with any of the following: Aurora A-targeted agent (excluding the MLN1117+TAK-659 arm); taxane-containing regimen (excluding the MLN1117+TAK-659 arm); spleen tyrosine kinase (SYK) inhibitor (MLN1117+TAK-659 arm only); or I phosphoinositide 3-kinase (PI3K) or serine/threonine kinase, also known as protein kinase B or PKB (AKT) inhibitor.

Main Criteria for Evaluation and Analyses:

The primary endpoints in Part 1 (dose escalation) are: the number (percentage) of patients who experience Cycle 1 dose-limiting toxicity (DLT) in Part 1; number (percentage) of patients with at least 1 treatment-emergent adverse event (TEAE) in Part 1; number (percentage) of patients with at least 1 ≥Grade 3 TEAE in Part 1; number (percentage) of patients with at least 1 treatment-emergent serious adverse event (SAE) in Part 1; and number (percentage) of patients with at least 1 dose modification due to AE in Part 1.

The primary endpoint in Part 2 (dose expansion) is the ORR (CR+PR) in patients with gastric or gastroesophageal junction adenocarcinoma when treated with MLN1117 in combination with TAK-659, alisertib, paclitaxel, or docetaxel.

Secondary endpoints for this study are the number (percentage) of patients with AEs, including SAEs from the first dose of study drug through 30 days after the last dose of study drug; overall drug exposure for each drug in each combination measured as the number (percentage) of patients with dose modifications due to AEs from the first dose of study drug through 30 days after the last dose of study drug in both Parts 1 and 2; measures of disease response (PFS, disease control rate, DOR, TTP, and OS) based on RECIST, Version 1.1; and summary statistics of the PK parameters maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the plasma concentration-time curve (AUC).

Statistical Considerations:

Part 1 (Dose Escalation)

There is no primary efficacy endpoint in Part 1 of the study. The secondary efficacy endpoint in Part 1 of the study is the ORR, defined as CR+PR, which will be presented in a listing.

The PK of MLN1117, TAK-659, and alisertib will be evaluated at prespecified time points during Part 1 (dose escalation).

Part 2 (Dose Expansion)

The primary efficacy endpoint for Part 2 is ORR (defined as CR+PR). The estimate of the RR will be presented with 2-sided 95% exact binomial CIs for each treatment arm. The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, Version 1.1.

The secondary endpoints in Part 2 of the study include PFS, disease control rate (CR+PR+SD), DOR, TTP, and OS. PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. An unstratified log-rank test will be used to compare the treatment arms with respect to PFS.

Disease control rate is defined as CR+PR+SD. The estimate of the disease control rate will be presented with 2-sided 95% exact binomial CIs for each treatment arm. The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, Version 1.1 [3].

DOR is defined as the time from the date of first documentation of a response to the date of first documentation of PD.

[redacted]

Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

TTP is defined as the time from the date of randomization to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

OS is defined as the time from the date of randomization to the date of death from any cause.

DOR, TTP, and OS will be analyzed using the Kaplan-Meier method. Unstratified long-rank tests will be performed for the comparisons between the 2 treatment arms.

Sparse PK of MLN1117, TAK-659, and alisertib will be evaluated at prespecified time points during Part 2 (dose expansion).

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the Safety population.

Sample Size Justification:
Part 1 (Dose Escalation)

The number of patients enrolled in this study will be driven initially by the dose escalation part and then by the dose expansion part. In Part 1 (dose escalation), approximately 15 patients may be enrolled in each combination treatment group, with potentially 3 to 6 patients in each dose cohort. Therefore, approximately 60 patients may be enrolled in the dose escalation phase.

Part 2 (Dose Expansion)

All patients who enter Part 2 of the study will be screened to determine whether or not their tumor tissue is positive for EBV (approximately 9% of patients with gastric cancer). An estimated 28 patients who are EBV positive will be assigned to treatment with TAK-659 in combination with MLN1117 (Cohort A). The sample size is estimated based on the following parameters: a 1-sided test at the significance level of alpha=0.05, power of 75%, a null hypothesis of RR=10%, and an alternative hypothesis of RR=25%. Based on a single proportion test, 28 evaluable patients need to be enrolled in Cohort A. For patients who are EBV negative, there will be 2 parts to the randomization phase. Patients initially will be randomized equally to 1 of the other treatment cohorts, 5 patients per group: MLN1117+alisertib (Cohort B), MLN1117+paclitaxel (Cohort C), or MLN1117+docetaxel (Cohort D). These patients will be assessed using a proportional weighted clinical utility function (allocating specific weights for CR, PR, stable SD, and PD. Initially the clinical utility function will assign weights for CR=5, PR=2, SD=1 and PD=0; after 6 months of having CR, PR, or SD, weights will increase to CR=6, PR=4, SD=2, and PD weighting will remain the same. Patients then will be randomized to treatment according to an adaptive randomization algorithm, which incorporates weighted clinical utility function. The resulting probability will continually be updated per accumulating data on the associations between the ORR and Bayesian stopping rules (defined below). Adaptive randomization will be applied to newly enrolling patients every 2 months based on cumulative data. The adaptive randomization will increase the opportunity for each patient to receive the most effective experimental treatment possible based on posterior probabilities. Up to an additional 25 patients may be enrolled in each treatment regimen during the part of the study with adaptive randomization. Based on simulation results, the sample size for Part 2 (the umbrella portion) may be between 61 and 90 patients. Therefore, a maximum number of 118 patients may be enrolled in the dose expansion phase.

ORR will be used as the efficacy benchmark: target 25% (0.25); undesirable 10% (0.1). Early stopping rules will be prespecified if there is a clear signal of efficacy or lack of efficacy. The stopping rules are as follows:

1. Achieve maximum sample size of each arm (30 patients).
2. Select an arm if Pr (RR>0.25/Data) >80% and Pr (RR>0.10)/Data) >90%.
3. Suspend accrual to an arm if Pr (RR≤0.10/Data) >80%.

The treatment arm(s) is/are chosen in relation to the efficacy bar prespecified (target and undesirable); therefore, it is possible to select multiple treatment arms per this study design.

[redacted]

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-FU	5-fluorouracil
5-HT_3	serotonin receptor subtype 3
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AKT	serine/threonine kinase, also known as protein kinase B or PKB
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUCt	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_\infty = AUC_t + C_{last}/\lambda_z AUC_\infty$
BID	bis in die (twice daily)
BSC	best supportive care
BUN	blood urea nitrogen
CL/F	apparent clearance after extravascular administration, calculated as dose/AUC_∞ after a single dose and as dose/AUC_τ after multiple dosing (at steady state)
C_{last}	last observed quantifiable plasma concentration
C_{max}	maximum observed plasma concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P-450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ECT	enteric-coated tablet
EOT	End of Treatment
FBG	fasting blood glucose
FDA	Food and Drug Administration
FIH	first-in-human

[redacted]

FLT-3	fms-related tyrosine kinase 3
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal
HbA1c	glycosylated hemoglobin
HDPE	high-density polypropylene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
ITAM	immunoreceptor tyrosine-based activation motif
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
λz	terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase
LDH	lactate dehydrogenase
LFT	liver function test
LMP2A	latent membrane protein 2A
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MLN1117	TAK-117
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PIK3CA / PI3Kα	phosphoinositide 3-kinase alpha isoform
PK	pharmacokinetic(s)
PO	per orum (oral, orally)
PPI	proton pump inhibitor
Pr	probability
PR	partial response
PTE	pretreatment event

[redacted]

[redacted]	[redacted]
QD	quaque die (once daily)
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum of longest diameters
SmPC	Summary of Product Characteristics
SOE	Schedule of Events
SYK	spleen tyrosine kinase
$t_{1/2}$	terminal elimination half-life
TAK-117	MLN1117
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
TTP	time to progression
ULN	upper limit of the normal range
US	United States
USPI	US prescribing information
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe, and/or TDC Americas, as applicable.

4.0 INTRODUCTION

4.1 Background

4.1.1 Gastric Cancer

Gastric cancer is the world's third leading cause of cancer mortality, responsible for 723,000 deaths in 2012 [http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 28 May 2015]. The vast majority of gastric cancers are adenocarcinomas, which can be further subdivided into papillary, tubular, mucinous (colloid), and poorly cohesive adenocarcinomas based on World Health Organization (WHO) classification. Recently, based on a comprehensive molecular evaluation of 295 primary gastric adenocarcinomas by The Cancer Genome Atlas project, molecular classification of gastric cancer to 4 subtypes has been proposed, which includes tumors positive for Epstein-Barr virus (EBV), microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. The PIK3CA (phosphoinositide 3-kinase alpha isoform) gene is found to be frequently mutated in gastric cancer, especially in tumors positive for EBV and microsatellite unstable tumors (with a mutation rate of 80% and 42%, respectively, in these 2 subtypes) [2].

Patients with advanced gastric cancer are treated with standard first-line options, including DCF (docetaxel, cisplatin, and 5-fluorouracil [5-FU]), which showed a cumulative 37% to 45.6% overall response rate (ORR), and 40% to 41.9% 1-year overall survival (OS) rate [4-8]; ECF (epirubicin, cisplatin and 5-FU), which showed an ORR of 40.2% to 46%, and 37% to 40.2% 1-year OS rate [4,7,9]; EOX (epirubicin, oxaliplatin, and capecitabine), which showed an ORR of 34.6 to 46% and OS of 6.9 to 8.8 months [10,11]; or FOLFOX (5-FU and oxaliplatin). As second-line agents, docetaxel, paclitaxel, and irinotecan are used to treat patients who have progressed on first-line treatment [12-14]. Recent Food and Drug Administration (FDA)-approved drug ramucirumab, a recombinant monoclonal antibody targeting the vascular endothelial growth factor receptor 2 (VEGFR-2), when combined with best supportive care (BSC), showed a 1.4-month median OS improvement (hazard ratio [HR]=0.78 [95% confidence interval (CI) 0.60 to 0.998, p=0.47]) as compared to placebo in combination with BSC (5.2 months vs 3.8 months). Median progression-free survival (PFS) was 2.1 months for ramucirumab+BSC compared with 1.3 months for placebo+BSC; the HR for PFS was 0.48 (95% CI 0.38 to 0.62, p<0.001) [15]. Ramucirumab in combination with paclitaxel also demonstrated improved median OS as compared to paclitaxel in combination with placebo (9.6 months vs 7.4 months), with an HR=0.81 (95% CI 0.68 to 0.96, p=0.017). In this trial, ORR was 28% (95% CI 23% to 33%) for the combination versus 16% (95% CI 13% to 20%) for paclitaxel+placebo [16]. Therefore, current management for advanced and metastatic gastric and gastroesophageal adenocarcinoma still remains suboptimal and there is a need for new and effective treatments for these patients.

4.1.2 Study Drugs

MLN1117 (TAK-117)

MLN1117 (also known as TAK-117) is an orally available, potent, and selective small molecule inhibitor of the class I phosphoinositide 3-kinase (PI3K) alpha isoform (PI3Kα). In human tumor mouse xenograft models harboring activating mutations for PI3Kα, MLN1117 inhibited pharmacodynamic markers of the PI3K pathway that correlate with strong tumor growth inhibition in a specific and dose-dependent manner. MLN1117 displayed consistent and predictable oral (PO) pharmacokinetic (PK) parameters across mice, rats, and monkeys. Toxicology studies were performed in rats and in monkeys. Detailed information regarding the nonclinical pharmacology and toxicology of MLN1117 may be found in the current version of the MLN1117 Investigator's Brochure (IB).

MLN1117 is being developed for the treatment of patients with malignancies in which the PI3K pathway is believed to contribute significantly to the pathologic process and response to standard therapies. MLN1117 is also being developed in combination with MLN0128 (a novel, highly selective, orally bioavailable adenosine 5' triphosphate-competitive inhibitor of the serine/threonine kinase referred to as the metabolic target of rapamycin) as a treatment for advanced nonhematologic malignancies. In addition, MLN1117 in combination with docetaxel as the second line of treatment in non-small cell lung cancer (NSCLC) is being evaluated in a phase1b/2 study.

In the phase 1, first-in-human (FIH) study (Study INK1117-001), MLN1117 is administered PO in 21-day treatment cycles of daily and intermittent dosing schedules. The study consists of a dose escalation phase and a dose-level expansion phase. The escalation phase will enroll approximately 120 patients with solid tumors. The expansion phase will enroll approximately 70 patients who have breast cancer or NSCLC. As of 22 June 2015, a total of 121 patients have received at least 1 dose of MLN1117. Most (68%) patients were women, and the median age was 61 years (range, 31-80 years). Of the 121 patients, 116 discontinued study drug treatment, including 83 (69%) who discontinued due to disease progression, 13 (11%) who discontinued due to ≥1 treatment-emergent adverse events (TEAEs), 10 (8%) who discontinued due to patient decision, and 10 (8%) who discontinued due to taking a medication prohibited per protocol, were lost-to-follow-up, or for other reasons. A total of 5 patients remained ongoing as of the clinical data cutoff. A tabular summary of the weekly dosing regimens administered as of 23 June 2014 is presented in Table 4.a

Table 4.a INK1117-001 Dosing Regimens

Weekly Dosing Regimen	Dose (mg)
QD	100, 150, 200, 300
QD on MWF	200, 300, 400, 600, 900, 1200
QD on MTW	200, 400, 600, 900
BID on MWF	300

BID=twice daily, MTW=Monday, Tuesday, and Wednesday, MWF=Monday, Wednesday, and Friday, QD=once daily, QW=each week.

[redacted]

In the PK analysis portion of this study, MLN1117 capsules were administered PO using 3 different dosing schedules: once daily (QD); 3 days each week (QW) of consecutive-day dosing (eg, Monday, Tuesday, and Wednesday [MTW] QW); and 3 days each week of every-other-day dosing (eg, Monday, Wednesday, and Friday [MWF] QW). The plasma PK of MLN1117 was evaluated in Study INK1117-001 for 24 hours after dosing of MLN1117 on Day 1 of Cycles 1 and 2, and during Week 2 of Cycle 1. Preliminary PK data suggest fast PO absorption following MLN1117 dosing, with a mean plasma terminal disposition half-life ($t_{½}$) of approximately 11 hours across cohorts. The extent of accumulation following QD dosing was low (accumulation ratio of approximately 1.2). Systemic exposures of MLN1117 increased with increasing dose over the 100 to 1200 mg dose range. There was a 9-fold increase in plasma exposure (area under the plasma concentration-versus-time curve [AUC] from zero to infinity [AUC_{∞}]) of MLN1117, with a 12-fold increase in dose from 100 to 1200 mg.

MLN1117 Clinical Safety

A total of 118 of the 121 patients (98%) overall experienced at least 1 TEAE as of the data cutoff date. Nine patients (7%) experienced ≥1 dose-limiting toxicity (DLT) in Cycle 1. A total of 106 patients (88%) had ≥1 TEAE that was considered by the investigator to be related to study drug, 64 (53%) had an adverse event (AE) that was severity ≥Grade 3, and 36 (30%) had at least 1 TEAE ≥Grade 3 that was considered by the investigator to be study drug-related. A total of 10 (8% of patients) on-study deaths were reported as of the data cutoff date, none of which was considered to be related to study drug.

AEs experienced by at least 10% of the 121 patients included nausea (60% of patients); vomiting (50%); fatigue (48%); diarrhea (45%); hyperglycemia (37%); decreased appetite (36%); constipation (31%); aspartate aminotransferase (AST) increased (28%); alanine aminotransferase (ALT) increased (23%); anemia (20%); cough, dehydration, dyspepsia, hypokalemia (17%, each); dyspnea (16%); abdominal pain, insomnia, weight decreased (15%, each); headache (13%); asthenia, back pain, dizziness, pyrexia (12%, each); stomatitis, urinary tract infection (11%); and peripheral edema (10%).

Protocol-defined DLTs in Cycle 1 of Study INK1117-001 have informed the selection of 900 mg MLN1117 as the proposed maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for the intermittent schedules (MWF QW and MTW QW). The MTD for the QD schedule is 150 mg. As of data cutoff, 13 DLT event terms were reported among 8 patients. The DLTs and dose assignments for these 8 patients were as follows: drug-induced liver injury (200 mg QD); increased ALT/AST (1 patient at 300 mg QD and 1 at 900 mg MWF QW); hyperosmolar state (900 mg MWF QW); nausea (900 mg MTW QW); decreased appetite (1200 mg MWF QW); hyperglycemia (1200 mg MWF QW); and concomitant events of diarrhea, nausea, vomiting, and hyperglycemia (1200 mg MWF QW). All events were considered to be at least possibly related to study drug. None of the DLTs resulted in permanent discontinuation of study drug.

Hyperglycemia was reported in 45 patients (37%) and increased blood glucose was reported in 1 additional patient. TEAEs of hyperglycemia were considered related to study drug in 44 patients (36%) overall. The 3 intermittent dosing schedules (MWF QW, MTW QW, and twice daily (BID)

[redacted]

MWF QW) were associated with the highest percentages (38%, 40%, and 41%, respectively) of patients with hyperglycemia TEAEs compared with the QD schedule (29%), regardless of causality. Serious adverse events (SAEs) of hyperglycemia were reported in 4 patients (2 each in the MWF QW and the BID MWF QW cohorts); all 4 events were considered possibly related to study drug and all but 1 resolved without sequelae after dose interruption (the final event was ongoing as of data cutoff). Concomitant SAEs of hyperosmolar state and diabetic ketoacidosis were reported in 1 patient (MWF QW schedule); both events were considered Grade 3 and possibly related to study drug but resolved without sequelae after dose interruption.

As of the clinical data cutoff and regardless of causality, 34 patients (28%) had elevations in AST, 28 patients (23%) had elevations in ALT, 6 patients (5%) had elevations in blood alkaline phosphatase, 6 patients (5%) had increased blood bilirubin, 5 patients (4%) had elevations in gamma-glutamyltransferase, 4 patients (3%) had transaminases increased, and 1 patient experienced drug-induced liver injury. A total of 10 patients (8%) had study drug-related ≥Grade 3 increased ALT; 6 patients (5%) had study drug-related ≥Grade 3 increased AST; 3 patients (2%) had study drug-related ≥Grade 3 increased transaminases; and 1 patient (1%), each, experienced study drug-related ≥Grade 3 hyperbilirubinemia and drug-induced liver injury with 200 mg QD. Three patients discontinued study drug due to TEAEs consistent with increased liver function tests: 1 patient who received MLN1117 in the 300 mg QD regimen, 1 in the 900 mg MTW QW regimen, and 1 in the 1200 mg MWF QW regimen. To date, the incidence of increased AST and ALT overall and regardless of causality, has been generally higher in patients receiving MLN1117 QD (42% and 38%, respectively) than the intermittent MWF (AST 28%, ALT 20%); MTW (AST 29%, ALT 20%); and BID MWF (AST 14%, ALT 18%) schedules. Further details regarding the clinical experience with MLN1117 may be found in the current version of the MLN1117 IB.

Based on the available safety information, 900 mg MTW QW was declared the MTD and RPD2. The MTW QW schedule is the one that will be tested in this study. The 900 mg dose is the highest dose to be tested in this study because it is the single-agent MTD.

In this study, stress-inducing agents, such as docetaxel, paclitaxel, and the investigational agents TAK-659 and alisertib (MLN8237), will be evaluated for combinability and efficacy with MLN1117 in 1 of 4 combination regimens in patients with advanced gastric or gastroesophageal junction adenocarcinoma.

Docetaxel and Paclitaxel

Paclitaxel is the first member of the taxane family (a drug class that acts by disrupting the microtubular network essential for cell division) to receive marketing approval for cancer treatment. Paclitaxel has demonstrated clinical activity both as single-agent therapy and in combination with other chemotherapeutic agents in a variety of cancer types, including breast cancer, NSCLC, ovarian cancer, and pancreatic cancer. In Japan, paclitaxel is commonly used in practice as second-line chemotherapy in patients with gastric cancer and adenocarcinoma of the gastroesophageal junction, and weekly paclitaxel therapy has yielded an ORR ranging from 21% to 24%, OS of 5 to 9.5 months, and has shown a good toxicity profile [12-14].

[redacted]

Docetaxel is the second member of the taxane family to receive marketing approval for cancer treatment and has shown significant clinical activity both as single-agent therapy and in combination with other chemotherapeutic agents in a wide range of solid tumors. Docetaxel, in combination with cisplatin and fluorouracil, is approved in the United States (US), Europe, and Japan for the treatment of patients with untreated, advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction. In addition, docetaxel alone is commonly used as second-line therapy in patients with locally advanced and metastatic gastric cancer.

Alisertib

Alisertib (MLN8237) is a selective, small molecule inhibitor of Aurora A kinase, a critical regulator of mitotic progression and is amplified/over-expressed in colon, breast and other cancers. Alisertib inhibited proliferation and induced phenotypes consistent with Aurora A inhibition in cultured cancer cells. Alisertib demonstrated antitumor activity in several experimental solid and hematologic human tumor models. The results of drug metabolism and PK studies have shown that alisertib has an acceptable absorption, distribution, metabolism, and excretion (ADME) profile. The toxicity of alisertib in both rats and dogs was consistent with the inhibition of Aurora A kinase. Detailed information regarding the nonclinical pharmacology and toxicology of alisertib may be found in the current version of the alisertib IB.

As of 29 March 2015, company-sponsored alisertib studies include 10 single-agent phase 1 studies; 2 single-agent, phase 1, drug-drug interaction (DDI) studies; 3 single-agent, phase 2 studies; 1 single-agent, phase 1/2 study; 1 single–agent, phase 3 study; and 5 combination studies (3 studies with paclitaxel, 1 study with docetaxel, and 1 study with either rituximab or rituximab+vincristine). A total of 1197 patients have been dosed with alisertib in company-sponsored clinical trials (including 36 patients from 2 company-sponsored, non-US investigational new drug [IND] studies in Japan). AEs observed to date (as of 29 March 2015) are generally reversible, dose-dependent, and are consistent with the pharmacologic profile of alisertib as an anti-mitotic agent with predominant effects in proliferative tissues. The more commonly observed (≥30% incidence) TEAEs from pooled data across the alisertib single-agent studies include: neutropenia (48%), anemia (47%), fatigue (46%), diarrhea (44%), alopecia (36%), stomatitis (32%), and nausea (31%). Central nervous system (CNS) effects, including transient dose-dependent somnolence and/or confusion, have also been observed. Alisertib has shown anti-tumor activity in the form of objective tumor responses and/or prolonged disease stabilization in a number of different tumor types, including solid tumors (small cell lung cancer [SCLC], ovarian, head/neck, NSCLC, liposarcoma, colorectal, and breast) and hematological tumors (peripheral T-cell lymphoma [PTCL], multiple myeloma, follicular lymphoma, diffuse large B-cell lymphoma [DLBCL], Burkitt's lymphoma, mantle cell lymphoma [MCL], and acute myeloid leukemia [AML]). Further details regarding the clinical experience with alisertib may be found in the current version of the alisertib IB.

TAK-659

TAK-659 is a reversible, potent, dual inhibitor of spleen tyrosine kinase (SYK) and fms-related tyrosine kinase 3 (FLT-3) being developed for oncology indications, the pathogenesis of a subset

of tumors being driven by SYK- and/or FLT-3-mediated signaling. In cultured human tumor cells, TAK-659 potently inhibited the growth of hematopoietic-derived cell lines, with a concentration producing half-maximal response (EC_{50}) ranging from 11 to 775 nM in sensitive cell systems. TAK-659 demonstrated antitumor activity in several experimental hematologic human tumor models. The results of drug metabolism and PK studies have shown that TAK-659 has an acceptable ADME profile. In nonclinical toxicology studies, target organ toxicities with TAK-659 were similar in rats and dogs and generally consistent with inhibition of SYK activity. Detailed information regarding the nonclinical pharmacology and toxicology of TAK-659 may be found in the current version of the TAK-659 IB.

As of 22 October 2015, 30 patients have been dosed with TAK-659 in the FIH study (Study C34001), including 16 patients with solid tumors and 14 patients with lymphoma. Ten patients have been enrolled in the 60 mg cohort, 4 in the 80 mg cohort, 9 in the 100 mg cohort, and 7 in the 120 mg cohort. One patient in the 60 mg cohort presented with Grade 3 AST elevation as a DLT. Four DLTs occurred in 120 mg cohort: Grade 4 lipase elevation, Grade 3 lipase elevation, Grade 3 generalized edema, and Grade 3 mucositis. In the 100 mg cohort, no patient presented with a DLT or Grade 3/4 TEAEs. Based on these data, the MTD of TAK-659 in a continuous QD schedule is 100 mg, and therefore, this is the initial dose to be used for patients allocated to Cohort A in this trial.

Table 4.b summarizes drug-related TEAEs reported in ≥10% of patients treated with TAK-659 as of the 22 October 2015 cutoff date.

Table 4.b TAK-659 Drug-Related Treatment-Emergent Adverse Events (≥10% of Patients) (N=30)

TEAE	All Grades, n (%)	≥Grade 3, n (%)
Fatigue	9 (30)	0
AST increased	8 (27)	1 (3)
Diarrhea	7 (23)	2 (7)
Anemia	5 (17)	4 (13)
Hypophosphatemia	5 (17)	3 (10)
ALT increased	4 (13)	0
ALP increased	4 (13)	0
Lipase increased	3 (10)	2 (7)
Nausea	3 (10)	0
Periorbital edema	3 (10)	0
Pneumonia	3 (10)	2 (7)
Maculo-papular rash	3 (10)	0

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, TEAE=treatment-emergent adverse event.

Other drug-related ≥Grade 3 TEAEs were generalized edema, neutropenia, pancytopenia, pericardial effusion, pyrexia, stomatitis, and *Pneumocystis jirovecii* pneumonia (1 patient each).

[redacted]

Five patients discontinued study treatment due to AEs, 1 of which (pneumonia in a patient receiving 80 mg TAK-659) was considered related to study drug. Seven patients died during the study; no deaths were considered related to TAK-659.

Three of eight patients with DLBCL achieved a response of partial response (PR). In the 3 evaluable patients with follicular lymphoma, 1 achieved a complete response (CR) and 2 achieved PR. Further details regarding the clinical experience with TAK-659 may be found in the current version of the TAK-659 IB.

4.2 Rationale for the Proposed Study

4.2.1 Rationale for Combining MLN1117 with Docetaxel, Paclitaxel, or Alisertib

Tumor cells exposed to different cytotoxic agents can respond to damage and stress by activating various repair and survival pathways, which may lead to the emergence of drug-resistant cells. One of these adaptive responses involves activation of the PI3K survival pathway [17] [18-20]. It was reported that protein kinase B (AKT) up-regulation increases resistance to several chemotherapeutic agents, in particular antimicrotubule agents such as paclitaxel and colchicine [21]. GDC-0941, a pan-PI3K inhibitor, was reported to enhance antitumor activity of docetaxel in human breast cancer models in vitro and in vivo by rapid induction of proapoptotic mechanisms [18]. Thus it has been hypothesized that the chemopotentiation potential of PI3K pathway inhibition can be exploited to maximize the effectiveness of cytotoxic cancer therapy. In addition, understanding the order of the administration of anti-cancer drugs may help in selecting optimal dosing schedules, can potentially impact antitumor outcome, and minimize any overlapping toxicities [22,23].

The antitumor activity of MLN1117+docetaxel was evaluated in a PIK3CA-mutated NCI-H1048 human small cell lung carcinoma (SCLC) xenograft model in female nude mice. The combination was well tolerated and resulted in robust increase of antitumor activity when compared to the vehicle treatment in mice bearing SCLC xenografts. Furthermore, MLN1117 in combination with docetaxel demonstrated significant and synergistic antitumor activity when MLN1117 was administered 24 hours after treatment with docetaxel compared with concomitant dosing of both compounds in an SCLC model NCI-H1048 (Report MLN1117-11258). In the PIK3CA-mutated gastric cancer model GA0098, the combination of docetaxel administered 24 hours before MLN1117 displayed an additive effect compared to either agent alone.

Combination of MLN1117 and alisertib tested on multiple dosing schedules led to enhanced antitumor activity in 2 human gastric cancer models (Hs 746T and NCI-N87) and resulted in additive effects as compared to respective single-agent therapy, prolonged tumor re-growth delay, and had acceptable tolerability (RPT-02978).Taken together, these results support clinical evaluation of MLN1117 in combination with alisertib, paclitaxel, or docetaxel in patients with advanced gastric or gastroesophageal adenocarcinoma, and in particular, in combination dosing regimens in which the chemotherapeutic agents are administered 24 hours before dosing of MLN1117.

[redacted]

4.2.2 Rationale for Combining MLN1117 with TAK-659

There is also growing evidence that SYK is a component of the cellular signaling cascade associated with EBV latency and transformation. EBV-positive tumors may express latent membrane protein 2A (LMP2A), which contains an immunoreceptor tyrosine-based activation motif (ITAM) domain. ITAM-mediated SYK activation has been shown to be essential to the LMP2A-induced tumorigenicity in EBV-driven tumor models for both EBV-associated lymphomas such as Burkitt's lymphoma, and EBV-associated solid tumors such as nasopharyngeal carcinoma [24]. Recently, this subtype (approximately 9%) of gastric cancer has been identified as positive for EBV with a high frequency of PIK3CA mutations [2], suggesting a role of SYK and PI3Kα in the pathogenesis of EBV-positive gastric cancer. Preliminary nonclinical evaluation of MLN1117 in combination with TAK-659 demonstrated acceptable tolerability and improved tumor growth inhibition compared to either of the single agents alone in 2 gastric cancer models (PHTXM-30Ga and PHTX-32Ga) (Report RPT-02977). Thus, this evidence may constitute a rationale for investigating the combination of MLN1117 and TAK-659 in the EBV-positive subset of patients with gastric adenocarcinoma.

[redacted]

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objective in Part 1 is:

- To determine the initial safety of MLN1117 when administered with each of the combination partners measured as the MTD or recommended Part 2 dose.

The primary objective in Part 2 is:

- To evaluate the ORR as the primary efficacy measure of MLN1117 in combination with each of the combination partners in patients with gastric or gastroesophageal junction adenocarcinoma.

5.2 Secondary Objectives

The secondary objective in Part 1 is:

- To evaluate initial activity for each combination.

The secondary objective in Part 2 is:

- To evaluate additional efficacy measures, such as PFS, disease control rate, duration of response (DOR), time to progression (TTP), and OS of MLN1117 in combination with each of the combination partners in patients with gastric or gastroesophageal junction adenocarcinoma.

The secondary objectives in Parts 1 and 2 are:

- To determine the RP2D.
- To evaluate the overall safety and tolerability of MLN1117 in combination with each of the combination partners.
- To evaluate the PK of MLN1117 when dosed in combination with alisertib, TAK-659, docetaxel, or paclitaxel, and to evaluate the PK of alisertib and TAK-659 when these agents are dosed in combination with MLN1117.

5.3 Tertiary/Exploratory Objectives

The exploratory objectives are:

- [redacted]
- [redacted]

[redacted]

6.0 STUDY ENDPOINTS

6.1 Primary Endpoints

The primary endpoints in Part 1 (dose escalation) are:

- The number and percentage of patients who experience Cycle 1 DLT in Part 1 of the study.
- Number (percentage) of patients with at least 1 TEAE in Part 1.
- Number (percentage) of patients with at least 1 ≥Grade 3 TEAE in Part 1.
- Number (percentage) of patients with at least 1 treatment-emergent SAE in Part 1.
- Number (percentage) of patients with at least 1 dose modification due to AE in Part 1.

The primary endpoint in Part 2 (dose expansion) is:

- The ORR (defined as CR+PR) in patients with gastric or gastroesophageal junction adenocarcinoma when treated with MLN1117 in combination with TAK-659, alisertib, paclitaxel, or docetaxel.

6.2 Secondary Endpoints

The secondary endpoints are:

- The number (percentage) of patients with AEs, including SAEs, from the first dose of study drug through 30 days after the last dose of study drug.
- Overall drug exposure for each drug in each combination measured as the percentage of patients with dose delays, dose reductions, and dose interruptions due to AEs from the first dose of study drug through 30 days after the last dose of study drug as measured in both Part 1 and Part 2.
- Measures of disease response (including PFS, disease control rate, DOR, TTP, and OS) based on the investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 [3].
- Summary statistics of the maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and AUC of MLN1117 and TAK-659 in Part 1, Cycle 1 Days 1 and 17 when MLN117 is administered in combination with TAK-659.
- Summary statistics of C_{max}, t_{max}, and AUC of MLN1117 and alisertib in Part 1, Cycle 1 Day 3 when MLN1117 is administered in combination with alisertib.
- Summary statistics C_{max}, t_{max}, and AUC of MLN1117 in Part 1, Cycle 1 Day 2 when MLN1117 is administered in combination with paclitaxel or docetaxel.

[redacted]

6.3 Exploratory Endpoints

The exploratory endpoints are:

- [redacted]
- [redacted]

[redacted]

7.0 STUDY DESIGN

7.1 Overview of Study Design

This is an open-label, multicenter, phase 1b study of MLN1117 in combination with TAK-659, alisertib, paclitaxel, or docetaxel in adult patients with locally advanced and metastatic gastric or gastroesophageal junction adenocarcinoma. The study consists of a dose escalation phase (Part 1) and a dose expansion phase (Part 2). The statistical design for the dose expansion consists of equal randomization and adaptive randomization phases. The study population in Part 1 (dose escalation phase) will consist of adult patients with advanced solid tumors (including but not limited to gastric or gastroesophageal junction adenocarcinoma) with no other effective therapeutic options available. The study population in Part 2 (dose expansion phase) will consist of patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (Stage IIIb or IV) who progress to 1 line of prior systemic chemotherapy. It is expected that approximately 149 to 178 patients will be enrolled in the study.

Part 1 (Dose Escalation)

During Part 1, the dose of MLN1117 will be escalated (planned dose levels of 300 mg, 600 mg, and 900 mg) according to a 3+3 dose escalation scheme (Section 9.3), while TAK-659, alisertib, paclitaxel, and docetaxel will be administered at a fixed dose and regimen until the MTD or recommended Part 2 dose are determined. Approximately 12 to 15 patients may be enrolled in each combination treatment arm, with potentially 3 to 6 patients in each dose cohort. Therefore, approximately 60 patients may be enrolled in the dose escalation phase. The patient allocation process is detailed in the Cohort Management Plan. Patients will be assigned in the optimal way to complete the next open dose level in each cohort. Once a dose level is open in 1 cohort, the first 3 patients will be allocated to this cohort before another cohort is open. Exceptions to this rule can be made based on specific rationale provided by the investigator and discussed during regular investigator teleconferences based on clinical, molecular, or other considerations. Serial PK samples will be collected at prespecified time points in Cycle 1 to characterize the PK of MLN1117 when given in each of the combination regimens, and the PK of alisertib and TAK-659 when given in combination with MLN1117. The schedule of PK sampling is provided in Appendix Table A and described in Section 10.4.15. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 [1]. DLTs are defined in Section 9.2.

At the end of the dose escalation phase in each treatment cohort, the overall safety and exposure will be evaluated to decide: (1) the recommended dose for Part 2 (not exceeding the MTD or maximally assessed dose) for each treatment cohort, and (2) if, based on the overall preliminary safety and exposure, any of the cohorts should not proceed into Part 2. The decision will be made by the Part 1 investigators and the sponsor and documented in minutes that will be distributed to Part 2 investigators and institutional review boards (IRBs).

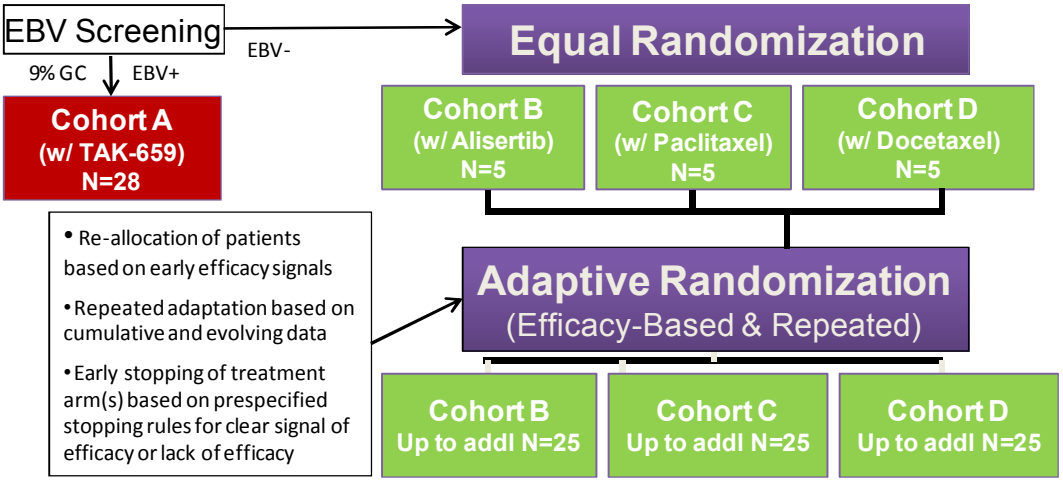
Part 2 (Dose Expansion)

All patients who enter Part 2 of the study will be screened to determine whether or not their tumor tissue is positive for EBV (approximately 9% of patients with gastric cancer). An estimated 28 patients who are EBV positive will be assigned to treatment with TAK-659 in combination with MLN1117 (Cohort A). Patients who are EBV negative initially will be randomized equally to 1 of the other treatment cohorts, 5 patients per group: MLN1117+alisertib (Cohort B), MLN1117+paclitaxel (Cohort C), or MLN1117+docetaxel (Cohort D). These patients will be assessed using a proportional weighted clinical utility function (allocating specific weights for CR, PR, stable disease [SD], and progressive disease [PD]). Patients then will be randomized to treatment according to an adaptive randomization algorithm, which incorporates a weighted clinical utility function. The resulting probability will continually be updated per accumulating data on the associations between the ORR and Bayesian stopping rules (defined in Section 14.1.2). Adaptive randomization will be applied to newly enrolling patients every 2 months based on cumulative data. The adaptive randomization will increase the opportunity for each patient to receive the most effective experimental treatment possible based on posterior probabilities. Up to an additional 25 patients may be enrolled in each treatment regimen. Based on simulation results, the sample size for Part 2 (umbrella portion) of the study may be between 61 and 90 patients. Therefore, a maximum number of 118 patients may be enrolled in the dose expansion phase.

ORR will be used as the efficacy benchmark: target 25% (0.25); undesirable 10% (0.1). Early stopping rules will be prespecified if there is a clear signal of efficacy or lack of efficacy. The stopping rules are as follows: (1) achieve maximum sample size of each arm (30 patients); (2) stop an arm if probability (Pr), Pr (response rate [RR]>0.25/Data) >80% and Pr (RR>0.10)/Data) >90%; (3) suspend accrual to an arm if Pr (RR≤0.10/Data) >80%. The treatment arm(s) is/are chosen in relation to the efficacy bar prespecified (target and undesirable); therefore, it is possible to select multiple treatment arms per this study design.

[redacted]

Figure 7.a Study Design for Part 2 of the Study



EBV=Epstein-Barr virus, GC=gastric cancer [2].

Radiological evaluations (CT scan or magnetic resonance imaging [MRI] as clinically indicated) will be employed to assess the status of the patient's underlying disease, and serial blood samples will be collected for tumor-specific markers. Disease response will be evaluated using the RECIST, Version 1.1 [3].

AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of MLN1117 when administered in combination with TAK-659, alisertib, paclitaxel, or docetaxel.

Sparse PK blood samples will be collected in Part 2 for all patients in all treatment cohorts to contribute to future population PK analysis of MLN1117, TAK-659, and alisertib. Samples will be obtained at prespecified time points as described in Appendix Table B and Table C, and in Section 10.4.15.

[redacted]

[redacted]

Patients may receive study drugs until they experience PD or unacceptable toxicity. The maximum duration of treatment will be 1 year for MLN1117, alisertib, and TAK-659, and 6 cycles for paclitaxel and docetaxel. Exceptions can be made for patients with clear clinical benefit after discussion between the investigator and the sponsor. If it is necessary to discontinue paclitaxel or docetaxel due to cumulative toxicity, it would be possible to continue treatment with MLN1117 as single agent. If it is necessary to discontinue MLN1117 for safety reasons, the patient should be withdrawn from the trial. For special circumstances, in which it is recommended that the patient continue only on the companion drug, agreement between the investigator and sponsor is required. Paclitaxel and docetaxel may be administered after Cycle 6 if the investigator and sponsor determine that the patient would derive benefit from continued treatment.

Patients will be followed for 30 days after the last dose of any study drug or until the start of subsequent antineoplastic therapy to permit the detection of any delayed treatment-related AEs. Patients who discontinue study drug treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks from End of Treatment (EOT) until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the discontinuation of study treatment, whichever occurs first. Patients will be followed for OS every 12 weeks until death or until 1 year after the last dose of study drug, whichever occurs first.

7.2 Number of Patients

Approximately 149 to 178 patients will be enrolled in this study from approximately 30 study centers in North America and Europe. Approximately 60 patients may be enrolled in Part 1 (dose escalation) and approximately 89 to 118 patients may be enrolled in Part 2 (dose expansion). Enrollment is defined as the time when the patient receives the first dose of any study drug.

In Part 1, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

In Part 2, patients who withdraw early and do not have a postbaseline response assessment will be replaced, unless they were withdrawn for PD.

7.3 Duration of Study

Patients will be followed for 30 days after the last dose of any study drug or until the start of subsequent alternative anticancer therapy to permit the detection of any delayed treatment-related AEs. Patients who discontinue study drug treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the discontinuation of study treatment, whichever occurs first. Patients will be followed for OS every 12 weeks until death or until 1 year after the

[redacted]

last dose of study drug, whichever occurs first. The final analyses for the clinical study report will be conducted after all patients enrolled in the study have had the opportunity to complete 6 cycles of treatment with study drug.

It is anticipated that the duration of this study will be 10 months for Part 1 (dose escalation), 24 months for Part 2 (dose expansion), 6 months for treatment, and 6 months for OS.

[redacted]

8.0 STUDY POPULATION

8.1 Inclusion Criteria

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

8.1.1 Part 1 and Part 2

1. Male or female patients aged 18 years or older at the time of consent.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to Appendix C) within 14 days before enrollment.
3. Adequate organ and hematologic function as evidenced by the following laboratory values within 14 days before enrollment:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
   - Platelet count $\geq 100 \times 10^9$/L.
   - Hemoglobin ≥9 g/dL (Transfusions are allowed to reach this hemoglobin level.).
   - Serum creatinine ≤1.5 times the upper limit of the normal range (ULN) or creatinine clearance ≥50 mL/min either as estimated by the Cockcroft-Gault equation (Appendix D) or based on urine collection (12 or 24 hours).
   - Total bilirubin ≤1.5×ULN.
   - AST and ALT ≤2.5×ULN.
4. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 1 highly effective method (see Appendix E) and 1 additional effective (barrier) method of contraception at the same time, from the time of signing the informed consent form through 30 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days), or for as long as mandated by local labeling for docetaxel and paclitaxel, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form through 30 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days), or for as long as mandated by local labeling for docetaxel and paclitaxel. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not

[redacted]

acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days), or for as long as mandated by local labeling for docetaxel and paclitaxel, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, during the entire study treatment period and through 120 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days) or for as long as mandated by local labeling for docetaxel and paclitaxel. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

5. 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.
6. Suitable venous access for the study-required blood sampling (ie, PK sampling, circulating tumor DNA).

8.1.2 Part 1 Only

2.1 A histologically confirmed diagnosis of advanced solid tumor, including but not limited to gastric or gastroesophageal junction adenocarcinoma.

2.2 Radiographically or clinically evaluable disease. Measurable disease as defined by RECIST, Version 1.1 is not required.

2.3 Relapsed or refractory patients with no effective therapeutic options available.

8.1.3 Part 2 Only

3.1 A histologically confirmed diagnosis of metastatic or locally advanced adenocarcinoma of the stomach or gastroesophageal junction (Stage IIIb or IV according to International Union Against Cancer [UICC] tumor, node, metastases [TNM] classification 7th edition [25]).

3.2 At least 1 measurable lesion per RECIST, Version 1.1 [3] by radiographic techniques (CT or MRI).

3.3 Receipt of 1 prior systemic chemotherapy regimen for advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction with documented PD.

3.4 Archived or fresh tumor biopsy samples obtained during screening sufficient for EBV testing and genotyping.

[redacted]

8.2 Exclusion Criteria

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

8.2.1 Part 1 and Part 2

1. Has received prior systemic anticancer therapies or other investigational agents within 2 weeks before the first administration of study drug or has failed to recover from the adverse drug effects of prior therapies (to ≤Grade 1 or to a level meeting inclusion criteria). For prior therapies with a half-life longer than 3 days, the interval must equal minimally 28 days before the first administration of study drug and the subject must have documented PD.
2. Radiotherapy within 14 days before enrollment.
3. Fasting glucose ≥130 mg/dL. Poorly controlled diabetes mellitus (glycosylated hemoglobin [HbA1c] >7.0%). Patients with a history of transient glucose intolerance due to corticosteroid administration are allowed.
4. Has received strong cytochrome P-450 (CYP) 3A4 inducers/inhibitors (Appendix F) within 7 days before the first administration of study drug or has conditions that require the concomitant use of CYP3A4 inducers/inhibitors during the course of the study.
5. For TAK-659 (Cohort A) only: Receiving treatment with medications that are known to be inhibitors or inducers of P-glycoprotein (P-gp; Appendix G). Baseline lipase >ULN. Patients not fulfilling these exclusion criteria can be enrolled in other cohorts (Part 1 only).
6. Has taken proton pump inhibitors within 7 days before the first administration of study drug or has conditions that require the concomitant use of proton pump inhibitors during the course of the study.
7. Signs of peripheral neuropathy ≥NCI CTCAE Grade 2.
8. Symptomatic brain metastases or brain metastases with a stable neurologic status for <2 weeks after completion of the definitive therapy and steroids.
9. Systemic infection requiring intravenous (IV) antibiotic therapy or other serious infection within 14 days before the first dose of study drug.
10. Known or suspected human immunodeficiency virus (HIV) positive or hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection. Testing for these agents is not required in the absence of clinical findings or suspicion.
11. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerability of orally administered study drug, including difficulty swallowing tablets; diarrhea >Grade 1 despite supportive therapy; or prior total gastrectomy.
12. Previous exclusion criterion #12 deleted in Amendment 1.

[redacted]

13. Clinically significant comorbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease, active central nervous system disease, or any other condition that could compromise the subject's participation in the study.
    - Known impaired cardiac function or clinically significant cardiac disease includes: evidence of currently uncontrolled cardiovascular conditions (including arrhythmias, angina, pulmonary hypertension, acute ischemia or active conduction system abnormalities); current history of New York Heart Association Class III or IV heart failure; acute myocardial infarction within 6 months before starting study drug; baseline QT interval corrected for heart rate (QTc) ≥Grade 1 according to NCI CTCAE Version 4.03 criteria; or abnormalities on baseline 12-lead ECG that are considered clinically significant per the investigator.
14. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.
15. Patients with bilirubin >ULN, or AST and/or ALT >1.5×ULN concomitant with alkaline phosphatase >2.5×ULN cannot be allocated to Cohort D (MLN1117+docetaxel) in Part 1 and are not eligible for Part 2 if they are also EBV negative.

8.2.2 Part 2 Only

2.1 Prior treatment with any of the following:

- An Aurora A-targeted agent (not eligible for randomization in Cohorts B, C, or D, but eligible for Cohort A if EBV positive).
- A docetaxel- or paclitaxel-containing chemotherapy regimen (not eligible for randomization in Cohorts B, C, or D, but eligible for Cohort A if EBV positive).
- An SYK inhibitor (MLN1117+TAK-659 [Cohort A] only).
- A PI3K or AKT inhibitor.

[redacted]

9.0 STUDY DRUG

9.1 Study Drug Administration

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

The dosing regimen for study drugs in each of the cohorts is outlined in the following sections.

9.1.1 MLN1117+TAK-659 (Cohort A)

MLN1117 will be administered PO QD for 3 days on (ie, Days 1, 2, 3; 8, 9, 10; 15, 16, 17; 22, 23, and 24) and 4 days off per week in each 28-day cycle. The dose of MLN1117 when administered in combination with TAK-659 as determined in Part 1 will be used in Part 2. TAK-659 will be administered PO at the MTD of 100 mg in a continuous QD dosing schedule in each 28-day cycle as determined in the FIH Study C34001. Please see Table 9.a for further information on dosing schedule for each cycle in Cohort A.

9.1.2 MLN1117+Alisertib (Cohort B)

MLN1117 will be administered PO QD for 3 days on (ie, Days 1, 2, 3; 8, 9, 10; 15, 16, 17; 22, 23, and 24) and 4 days off per week in each 28-day cycle. The dose of MLN1117 when administrated concomitantly with alisertib will be determined in the Part 1 dose escalation phase and used in the Part 2 dose expansion phase. Alisertib will be administered PO at 40 mg BID for 3 days on (ie, Days 1, 2, 3; 8, 9, 10; 15, 16, and 17) and 4 days off per week on Weeks 1-3, and 1 week off in each 28-day cycle. Please see Table 9.b for further information on dosing schedule for each cycle in Cohort B.

9.1.3 MLN1117+Paclitaxel (Cohort C)

MLN1117 will be administered PO QD for 3 days on (ie, Days 2, 3, 4; 9, 10, 11; 16, 17, 18; 23, 24, and 25) and 4 days off per week in each 28-day cycle. The dose of MLN1117 when administrated concomitantly with paclitaxel will be determined in the Part 1 dose escalation phase and used in the Part 2 dose expansion phase. Paclitaxel will be administered IV at 80 mg/m^2 once weekly on Days 1, 8, and 15, and 1 week off, in each 28-day cycle. Please refer to the paclitaxel label or prescribing information (US Prescribing Information [USPI] or Summary of Product Characteristics [SmPC]) for further details regarding administration, and Section 9.6.1 for paclitaxel premedications. Please see Table 9.c for further information on dosing schedule for each cycle in Cohort C.

9.1.4 MLN1117+Docetaxel (Cohort D)

MLN1117 will be administered PO QD for 3 days on (ie, Days 2, 3, 4; 9, 10, 11; 16, 17, and 18) and 4 days off per week in each 21-day cycle. The dose of MLN1117 when administrated concomitantly with docetaxel will be determined in the Part 1 dose escalation phase and used in

the Part 2 dose expansion phase. Docetaxel will be administered IV at 75 mg/m^2 on Day 1 once every 3 weeks in a 21-day cycle. Please refer to the docetaxel USPI or SmPC for further details regarding administration, and Section 9.6.1 for docetaxel premedications. Please refer to Table 9.d for further information on dosing schedule for each cycle in Cohort D.

[redacted]

Table 9.a Cohort A: MLN1117+TAK-659 Dosing Schedule

Cohort A	28-Day Cycle, All Cycles																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
MLN1117	x	x	x					x	x	x					x	x	x					x	x	x				
TAK-659	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 9.b Cohort B: MLN1117+Alisertib Dosing Schedule

Cohort B	28-Day Cycle, All Cycles																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
MLN1117	x	x	x					x	x	x					x	x	x					x	x	x				
Alisertib	xx	xx	xx					xx	xx	xx					xx	xx	xx											

Table 9.c Cohort C: MLN1117+Paclitaxel Dosing Schedule

Cohort C	28-Day Cycle, All Cycles																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
MLN1117		x	x	x					x	x	x					x	x	x					x	x	x				
Paclitaxel	x							x							x													

Table 9.d Cohort D: MLN1117+Docetaxel Dosing Schedule

Cohort D	21-Day Cycle, All Cycles																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
MLN1117		x	x	x					x	x	x					x	x	x			
Docetaxel	x																				

[redacted]

The study drug that is administered orally, such as MLN1117, TAK-659, and alisertib, should be taken on an empty stomach, at least 1 hour before and no sooner than 2 hours after a meal. Each tablet should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the tablets. Patients should swallow the study medication whole. The study medication should not be chewed before swallowing. Administration of the tablets will be guided by the dosing tables included above and also in the Pharmacy Manual.

Patients should be instructed to take their study medication at approximately the same time each day and not take more than the prescribed dose at any time. On visit days, patients should be instructed to hold their dose until predose assessments are performed (unless otherwise specified for visits in which holding the dose is not needed, ie, in Part 2 when patients are instructed to take the dose of study drug at home and report to the study site according to Appendix Table B and Table C to enable collection of sparse PK samples). In the event that a patient fails to take study drug(s) on 1 day, the patient must not make dose adjustments to account for the missed dose on subsequent days, for example, by taking a double dose of study drug(s) on the following day. Patients should record any skipped doses in their dosing diary (see the Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

If severe emesis or stomatitis prevents the patient from taking a dose of study drug(s), that dose will be skipped. If emesis occurs after study medication ingestion, patients should simply adhere to the dosing schedule and continue dosing at the next scheduled time with the prescribed dosage. Patients should not take a repeat dose following emesis after study medication ingestion. Patients should record the time of the emesis in their dosing diary (see the Study Manual).

In cohorts where both study drugs are administered orally (Cohort A: MLN1117+TAK-659 and Cohort B: MLN1117+alisertib), there is no requirement for a specific sequence of administration for each of the study drugs in both cohorts. For patients in Cohort B, the 2 daily doses of alisertib should be separated by approximately 12 hours. Patients will be advised to establish a routine based on their own preference and adhere to the same dosing routine as much as possible.

9.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03 [1]. These criteria are provided in the Study Manual. DLT will be defined as any of the following events occurring during Cycle 1 in Part 1 that are considered by the investigator to be at least possibly related to either or both of the study drugs (MLN1117, TAK-659, alisertib, paclitaxel, or docetaxel) in an assigned combination regimen:

- Grade 4 neutropenia (ANC<500 cells/mm^3) lasting more than 7 consecutive days.
- ≥Grade 3 neutropenia (ANC<1000 cells/mm^3) with fever and/or infection, where fever is defined as a single temperature ≥38.3°C (101°F) or sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
- Grade 4 thrombocytopenia lasting more than 7 consecutive days.
- Grade 3 thrombocytopenia of any duration accompanied by clinically significant bleeding.

[redacted]

- A platelet count <10,000/mm^3 at any time.
- Grade 3 or greater nonhematologic toxicity with the following exceptions:
  - Grade 3 arthralgia/myalgia.
  - Grade 3 fatigue that lasts less than 1 week.
  - Grade 3 nausea and/or emesis that can be controlled to ≤Grade 1 or baseline in 7 days with the use of optimal antiemetic prophylaxis (defined as an antiemetic regimen that employs both a 5-HT antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - Grade 3 diarrhea that can be controlled to ≤Grade 1 or baseline in 7 days with optimal supportive therapy.
  - Grade 2 fasting hyperglycemia lasting ≤14 days with optimal treatment or Grade 3 fasting hyperglycemia lasting ≤24 hours with optimal treatment.
  - Grade 3 rash lasting ≤7 days with optimal treatment that includes topical steroid treatment, PO antihistamines, and pulse PO steroids, if necessary.
  - Any other Grade 3 nonhematologic toxicity that can be controlled to ≤Grade 1 or baseline in 7 days with appropriate treatment. In this setting, a course of action will be determined jointly by the investigators and the sponsor clinician.
- Delay in the initiation of the subsequent cycle of therapy by more than 7 days due to treatment-related hematological or nonhematologic toxicities.
- Greater than or equal to Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug(s) and dose-limiting. In this setting, a course of action will be determined jointly by the investigators and the sponsor clinician.

Although DLT may occur at any point during treatment, only DLT occurring during Cycle 1 of treatment in Part 1 (dose escalation) will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients in both Parts 1 and 2 will be monitored through all cycles of therapy for treatment-related toxicities.

Patients experiencing DLT in Cycle 1 may continue in the study provided they are deriving clinical benefit, but will be administered reduced doses of MLN1117 and/or the combination agent as appropriate.

9.3 Dose Escalation Rules (Part 1)

A standard 3+3 dose escalation scheme will be used to determine the MTD of MLN1117 when administered in combination with 1 of the combination partners (ie, TAK-659, alisertib, paclitaxel, or docetaxel), each administered at a fixed dose and schedule. The initial MLN1117 dose will be 300 mg administered PO QD following the 3-days-on and 4-days-off weekly schedule. The next planned dose levels will be 600 mg and then 900 mg. However, alternative escalation in response to evolving safety, PK, and other relevant data is permissible, following discussion and agreement

[redacted]

between investigators and the sponsor. This includes evaluation of intermediate dose levels, expansion of an existing dose level, and alternative regimens/schedule of MLN1117 if appropriate. In the event that the initial dose of 300 mg is determined to be intolerable, de-escalation of the dose in 100-mg decrements may be considered, or a decision may be made jointly by the investigators and sponsor to discontinue the dose escalation for that cohort.

Dose escalation will be based on DLT as determined in Cycle 1. Rules for dose escalation based on Cycle 1 DLT include:

1. If 0 of 3 patients experience DLT, dose escalation will proceed to the next higher dose level, at which 3 patients will be enrolled.
2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.
3. Dose escalation will continue if 1 of 6 patients experiences DLT.
4. If 2 or more patients in any dose level experiences DLT, dosing will stop, and the previous dose level will be considered the MTD.
5. If 0 of 3 or 1 of 6 patients experience DLT at the dose level of 900 mg MLN1117, no further escalation will occur and 900 mg will be considered the maximum administered dose (MAD).

During the dose escalation phase, patients not receiving at least 75% of the MLN1117 dose for reasons other than DLT in Cycle 1 will be replaced within the cohort.

The MTD is defined as the highest dose level of MLN1117 when administered in combination with the combination agent at which no more than 1 of 6 patients experiences a DLT during the first cycle of therapy in Part 1 (dose escalation). Although toxicities determined to be related or possibly related to the combination agent in each cohort will not directly influence the determination of the MTD for MLN1117, the determination of the recommended dose for Part 2 will take into account the frequency and severity of non-MLN1117 drug-related AEs and dose modification of the combination agents during Cycle 1 and beyond.

The RP2D of MLN1117 will be determined at the end of the trial (Part 1 and Part 2) on the basis of the totality of safety, tolerability, PK, dose modifications, and preliminary efficacy data (if available). The RP2D will not exceed the MTD.

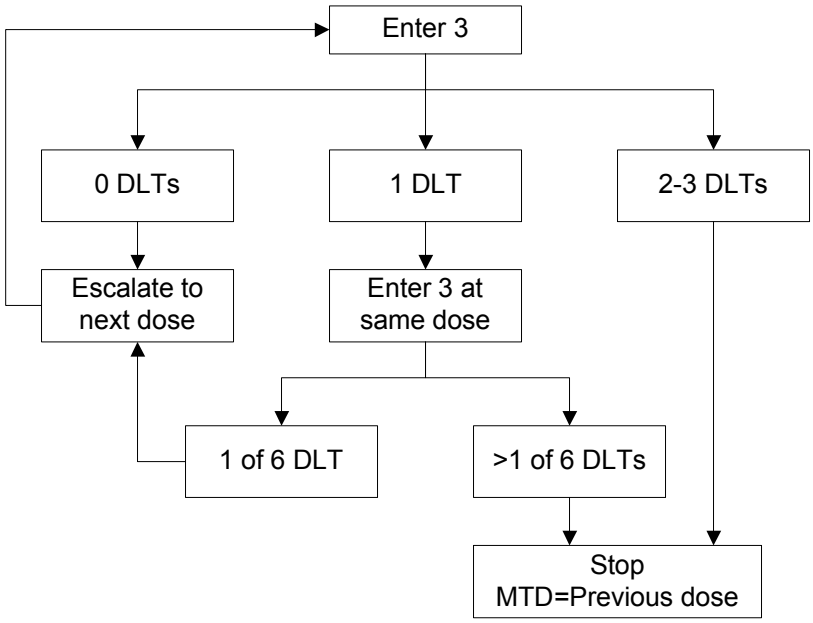
While the primary dose escalation schema (see Figure 9.a) is designed to determine a classical Cycle 1-based MTD, dose escalation may be halted at any time after consultation between the investigators and sponsor clinician if cumulative toxicity beyond Cycle 1 indicates that a given dose exceeds a tolerable recommended Part 2 dose.

Treatment with MLN1117 will be administered on a weekly schedule that includes 3 consecutive dosing days per week. During dose escalation, a reduction in the number of treatment days per week (eg, reducing dosing days from 3 to 2 days or further to 1 day) while maintaining the same dose may be considered as an alternative to reducing to a lower dose when dose de-escalation is indicated. This decision will be made jointly by investigators and the sponsor project clinician.

[redacted]

Although dose escalation is planned for MLN1117 only when the combination agent in each cohort is administered with a fixed dose and schedule, in the event that the first dose level of any cohort is not feasible because of the occurrence of DLT in more than 1 of 6 patients or in case of frequent occurrences of dose modification of the combination agent in Cycle 1 and/or Cycle 2 and beyond, upon discussion and agreement between investigators and the sponsor project clinician (or designee), the fixed dose of the combination agent could be reset at a lower dose (eg, -1 dose according to Table 9.e) for the purpose of further evaluation and determination of the MLN1117 MTD/recommended Part 2 dose/RP2D. For alisertib, which will be administered in a 3-days-on and 4-days-off schedule, reducing the number of dosing days per week instead of reducing the dose level could be considered.

Figure 9.a Dose Escalation Algorithm



DLT=dose-limiting toxicity, MTD=maximum tolerated dose.

9.4 Dose Modification Guidelines

In both Part 1 (dose escalation) and Part 2 (dose expansion) of the study, patients will be evaluated according to the Schedule of Events (Appendix A) for each of the 4 cohorts for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE, Version 4.03 [1]. The causal relationship of each AE should be assessed in relation to MLN1117 and to the combination agent in each cohort so that dose modifications can be made accordingly. Administration and dose adjustment of docetaxel (Cohort D) or paclitaxel (Cohort C) will follow applicable prescribing information, the guidance on dose modification (Section 9.4.4.3), and the guidance on the management of clinical events (see Section 9.8). Minimum requirements described in the docetaxel and paclitaxel prescribing information must be met before starting the next cycle or dose of docetaxel and paclitaxel treatment (see

[redacted]

Section 9.4.4.2). Dose modification guidelines for hematologic and nonhematologic toxicities are described below for both study drugs in each of the combination cohorts based on the type and severity of AEs, causality determination by investigators, and safety and tolerability profiles of each of the study drugs. Further clarification can be obtained in consultation with the sponsor clinician (or designee).

Per dose modification guidelines, patients who have the study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE but may either maintain the same dose level or have doses of study drug reduced (dose reduction) by at least 1 dose level. When a dose reduction of MLN1117 occurs, the MLN1117 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation (Part 1). During Part 2, depending on the recommended Part 2 dose determined during Part 1, MLN1117 dose reduction will follow, in general, a decrement of 300 mg, or a decrement of 100 mg for doses ≤300 mg. If initial dose adjustment does not provide sufficient relief, the dose of MLN1117 can be further reduced if the treating physician considers that the patient is benefiting from study treatment and may benefit at a further reduced dose of MLN1117. Up to 2 dose level reductions of MLN1117 due to AEs are generally recommended. If more than 2 dose reductions of MLN1117 (below those presented in Table 9.e) are needed to manage MLN1117-related AEs, discontinuation of treatment should be considered unless the treating physician, in consultation with the sponsor (or designee), feels the patient may benefit from continued study treatment after resolution of AEs to <Grade 1 or baseline.

For Cohort A, the MTD of TAK-659 was determined to be 100 mg in a continuous QD dosing schedule in each 28-day cycle (Study C34001, a FIH dose-escalation study of TAK-659 in patients with advanced solid tumor and lymphoma) (see Section 4.1.2). The dose reduction of TAK-659 will, in general, follow a decrement of 20 mg (Table 9.e).

For Cohorts B, C, and D, dose reduction levels for alisertib, paclitaxel, and docetaxel are described in Table 9.e for AEs that are attributed to each of the combination agents. Requirements for dose reduction below those presented in Table 9.e should prompt withdrawal of the patient from the study.

Table 9.e Dose Reduction Levels for MLN1117 and Combination Partners

Dose Reduction Levels	MLN1117	TAK-659	Alisertib	Paclitaxel	Docetaxel
RP2D/standard dose	RP2D TBD	100 mg (a)	40 mg	80 mg/m^2	75 mg/m^2
(–) 1 dose level	RP2D-300 mg (b)	80 mg	30 mg	65 mg/m^2	60 mg/m^2
(–) 2 dose level	RP2D-600 mg (b)	60 mg	20 mg	50 mg/m^2	45 mg/m^2

The need for dose reductions below those stated in this table should result in withdrawal of the patient from the study.
FIH=first in human, MTD=maximum tolerated dose, RP2D=recommended phase 2 dose, TBD=to be determined.
(a) The MTD of TAK-659 determined in Study C34001, a FIH dose escalation study of TAK-659 in advanced solid tumor and lymphoma.
(b) MLN1117 dose reduction will follow, in general, a decrement of 300 mg, or a decrement of 100 mg for doses ≤300 mg, depending on the MTD/recommended Part 2 dose as determined in Part 1.

[redacted]

If the dose of 1 study drug in a combination regimen is delayed because of toxicity attributed to its use, the dose of the other study drug in the combination regimen is to be administered as scheduled.

9.4.1 Intrapatient Dose Escalation (Part 1)

Once the recommended Part 2 dose of MLN1117 is determined, all patients in Part 1 who have received MLN1117 and another combination agent at a lower dose for a minimum of 2 cycles, in the absence of PD or unacceptable treatment-related toxicity per the investigator, may dose escalate to the recommended Part 2 dose of the assigned treatment cohort at the investigator's discretion and with the sponsor's approval. Patients in whom an increase in the dose of MLN1117 is being considered must have treatment-related AEs resolved to ≤Grade 1 or baseline or to a level that is acceptable to the investigators (nonhematologic toxicity must be ≤Grade 2, and hematologic toxicities must be less than the minimal requirement for starting a new cycle of treatment).

9.4.2 Intrapatient Dose Reduction(Part 1, Cycle 1)

Intrapatient dose reductions of MLN1117 are not permitted during Part 1 Cycle 1 unless the patient experiences a DLT attributed to MLN1117. DLT is defined in Section 9.2. If a patient experiences a DLT during Part 1 Cycle 1, treatment should be held, and the event counted toward the assessment of MTD for the given cohort. Patients experiencing DLT in Part 1 Cycle 1 may continue in the study upon resolution of the toxicity; however, the dose of MLN1117 (in combination with other combination agents) will be reduced by at least 1 dose level (or reduced by a 100-mg decrement if the patient is receiving the first dose level). Patients who receive a reduced dose of MLN1117 during Cycle 1 for reasons other than DLT will be replaced for DLT evaluation and dose escalation. Dose delay and dose reduction of any of the combination partners, and dose modification are allowed in Cycle 1 during Part 1 (see Section 9.4.3 and Section 9.4.4, which includes paclitaxel and docetaxel retreatment criteria). Frequency of dose delay and reduction of other combination agents will be taken into account in determining the recommended Part 2 dose and the RP2D for MLN1117 when administered in combination with these agents.

9.4.3 Dose Modification Guideline for Cohort A (MLN1117+TAK-659)

Please refer to Table 9.f for dose delay and reduction recommendations for hematologic toxicities and Table 9.g for nonhematologic toxicities for patients treated with MLN1117+TAK-659 in Cohort A. When TEAEs occur, the causality in relation to the study drug(s) will be determined by the investigators and dose modification will be applied to 1 or both study drugs determined to be the cause or possibly the cause of the AEs. When the dose of MLN1117 and/or TAK-659 is withheld based on the following criteria (Table 9.f and Table 9.g), clinical and laboratory re-evaluation should be repeated at least weekly or more frequently until the toxicity resolves to ≤Grade 1, baseline, or to a level considered acceptable by the investigator. Upon resolution of the toxicity, MLN1117 and/or TAK-659 may be reinitiated either at the same dose level or at a reduced dose level. In events where there are transient laboratory value abnormalities that, based on investigator assessment, are considered to be not clinically significant or related to disease and

not the drug, continuation of therapy without following the dose modification guideline is permissible upon discussion with the sponsor.

When a TEAE is likely drug-related, but it is difficult to determine to which study drug the TEAE is related, relatedness or possible relatedness will be assigned to both study drugs and dose modification made for both study drugs per the guideline below. After dose reduction of both study drugs, if the same event does not reoccur, or occurs at a level considered by the investigator to be not clinically significant, dose re-escalation of 1 study drug (while maintaining the other study drug at the reduced dose) could be explored with caution and close monitoring at the investigator's discretion, in consultation with the sponsor project clinician (or designee).

There are no separate criteria for beginning or delaying the subsequent cycles for Cohort A.

Table 9.f Dose Modification Guidelines for Hematologic Toxicities for Cohort A (MLN1117+TAK-659)

NCI CTCAE Grade	Description	Dose Modification for MLN1117	Dose Modification for TAK-659
Neutropenia			
1 or 2	ANC <1500 to 1000/mm^3; <1.5 to 1.0×10^9/L	No change. Continue MLN1117 at same dose and schedule.	No change. Continue TAK-659 at same dose and schedule.
3	ANC <1000 to 500/mm^3; <1.0 to 0.5×10^9/L	Hold MLN1117 until ANC ≥1500/mm^3, then restart MLN1117. If resolved in ≤7 days, maintain the same dose of MLN1117. If resolved in >7 days, reduce dose by 1 level.	Hold TAK-659 until ANC ≥1500/mm^3, then restart TAK-659. If resolved in ≤7 days, maintain the same dose of TAK-659. If resolved in >7 days, reduce dose by 1 level.
4	ANC <500/mm^3; <0.5×10^9/L	Hold MLN1117 until ANC ≥1500/mm^3, then restart MLN1117 at a reduced dose by 1 level.	Hold TAK-659 until ANC ≥1500/mm^3, then restart TAK-659 at a reduced dose by 1 level.
Other	Febrile Neutropenia ANC <1000/mm^3 and fever defined as a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour), OR ANC <1000/mm^3 with systemic infection	Hold MLN1117 until ANC ≥1500/mm^3 and fever and infection are resolved, then restart MLN1117 at a reduced dose by 1 level.	Hold TAK-659 until ANC ≥1500/mm^3 and fever and infection are resolved, then restart TAK-659 at a reduced dose by 1 level.

Footnotes are on last table page.

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Table 9.f Dose Modification Guidelines for Hematologic Toxicities for Cohort A (MLN1117+TAK-659) (continued)

NCI CTCAE Grade	Description	Dose Modification for MLN1117	Dose Modification for TAK-659
Thrombocytopenia			
1 or 2	PLT 50,000 to 100,000/mm^3; <50 to 100×10^9/L	No change. Continue MLN1117 at same dose and schedule.	No change. Continue TAK-659 at same dose and schedule.
3	PLT 25,000 to 50,000/mm^3; <25 to 50×10^9/L	Hold MLN1117 until PLT ≥100,000/mm^3 or baseline; then restart MLN1117. If resolved in ≤7 days, maintain the same dose of MLN1117. If resolved in >7 days, reduce dose by 1 level.	Hold TAK-659 until PLT ≥100,000/mm^3 or baseline; then restart TAK-659. If resolved in ≤7 days, maintain the same dose of combination agent. If resolved in >7 days, reduce dose by 1 level.
4	PLT <25,000/mm^3; <25×10^9/L	Hold MLN1117 until PLT ≥100,000/mm^3 ; When resolved, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).	Hold TAK-659 until PLT ≥100,000/mm^3. When resolved, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).
Other	PLT <10,000 cells/mm^3 or clinically significant bleeding	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor. If the patient's study treatment is not discontinued, then the MLN1117 dose will be reduced to at least 1 dose level lower when PLT ≥100,000/mm^3 and clinically significant bleeding is completely resolved.	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor. If the patient's treatment is not discontinued, then the TAK-659 dose will be reduced to at least 1 dose level lower when PLT ≥100,000/mm^3 and clinically significant bleeding are completely resolved.
Anemia			
3	Hgb <8.0 g/dL not due to bleeding; transfusion indicated	Hold MLN1117 until Hgb ≥9.0 g/dL; restart MLN1117 at same dose. In case of repeat occurrence at a reduced dose of TAK-659, MLN1117 will be reduced by 1 level.	Hold TAK-659 until Hgb ≥9.0 g/dL. If resolved in ≤7 days, maintain the same dose of TAK-659. If resolved in >7 days, reduce dose by 1 level.

Footnotes are on last table page.

Table 9.f Dose Modification Guidelines for Hematologic Toxicities for Cohort A (MLN1117+TAK-659) (continued)

NCI CTCAE Grade	Description	Dose Modification for MLN1117	Dose Modification for TAK-659
Anemia (continued)			
4	Hgb <6.5 g/dL not due to bleeding; life-threatening consequences; urgent intervention indicated	Hold MLN1117 until Hgb ≥9.0 g/dL. Consider discontinuation if anemia is attributable to the study drugs. If multifactorial, restart MLN1117 at same dose (with a reduced dose of TAK-659), or restart at a dose reduced by at least 1 level.	Hold TAK-659 until Hgb ≥9.0 g/dL. When resolved, consider discontinuation or continue at a reduced dose by at least 1 level.

ANC=absolute neutrophil count, Hgb=hemoglobin, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, PLT=platelets.

Table 9.g Dose Modification Guidelines for Nonhematologic Toxicity for Cohort A (MLN1117+TAK-659)

NCI CTCAE Grade	MLN1117 Dose Modification	TAK-659 Dose Modification
Hyperglycemia		
Grade 2 (Fasting glucose value >160 to 250 mg/dL; fasting glucose value >8.9 to 13.9 mmol/L)	Continue MLN1117 at same dose. Refer to Section 9.8.2 for guidelines on hyperglycemia management.	Continue TAK-659 at same dose.
Grade 3 (>250 to 500 mg/dL; >13.9 to 27.8 mmol/L; hospitalization indicated)	Hold MLN1117 until hyperglycemia ≤Grade 2. Optimize antihyperglycemic therapy and resume MLN1117 based on timing of recovery. • ≤1 week: resume MLN1117 at same dose and schedule. • >1 but ≤2 weeks or recurrent with antihyperglycemic treatment: reduce MLN117 dose to the next lower dose level for all subsequent cycles. • >2 weeks: stop MLN1117 and discontinue subject from study.	Continue TAK-659 at same dose and schedule.
Grade 4 (>500 mg/dL; >27.8 mmol/L; life-threatening consequences)	Hold MLN1117 until hyperglycemia ≤Grade 2. • ≤1 week: reduce MLN117 dose to the next lower dose level for all subsequent cycles. • >1 week: discontinue.	Hold TAK-659 until hyperglycemia improves to ≤Grade 2; then continue at same dose and schedule.

Footnotes are on last table page.

Table 9.g Dose Modification Guidelines for Nonhematologic Toxicity for Cohort A (MLN1117+TAK-659) (continued)

NCI CTCAE Grade	MLN1117 Dose Modification	TAK-659 Dose Modification
Asymptomatic serum lipase increase		
Grade 3 serum lipase increase accompanied by ≥Grade 3 serum amylase increase; OR Grade 4 serum lipase increase	Maintain the same dose/regimen of MLN1117 if determined to be unrelated.	Hold TAK-659 until resolution to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2), then restart TAK-659 at a reduced dose by 1 level.
AST/ALT		
Grade 3 elevation of single enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 2)	Maintain the dose of MLN1117 with close monitoring.	Maintain the dose of TAK-659 with close monitoring.
Grade 3 elevation of both AST and ALT	Hold MLN1117 until AST and ALT decrease to Grade 1. Restart MLN1117 at the same dose if resolved within 7 days, or reduce by 1 level if resolution is >7 days. If concomitant bilirubin elevation >Grade 1 attributable to drug toxicity, discontinue treatment.	Hold TAK-659 until AST and ALT decrease to Grade 1. Restart TAK-659 at the same dose if resolved within 7 days or reduce by 1 level if resolution is more than 7 days.
Grade 4 elevation of AST and/or ALT	Hold MLN1117 until AST and ALT decrease to Grade 1. Restart MLN1117 at a reduced dose by 1 level. If concomitant bilirubin elevation >Grade 1 attributable to drug toxicity, discontinue treatment.	Hold TAK-659 until AST and ALT decrease to Grade 1. Restart TAK-659 at a reduced dose by 1 level.
<u>All other Grade 3 nonhematologic toxicities with the exception of:</u> • Grade 3 nausea, vomiting, and diarrhea resolved to ≤Grade 1 or baseline within 1 week with optimal antiemetics and antidiarrheals following SOC. • Transient Grade 3 fatigue (lasting <1 week). • Grade 3 rash lasting ≤7 days with optimal treatment. • Any other Grade 3 nonhematologic toxicity that can be controlled to ≤Grade 1 or baseline in 1 week with appropriate treatment in 7 days.	Hold MLN117 if determined to be related to MLN1117 until resolution to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then dose reduce by 1 dose level. • If recurred, then dose reduce by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as ≥Grade 3 for more than 14 days despite temporary disruption of study drug.	Hold TAK-659 if determined to be related to TAK-659 until resolution to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then dose reduce by 1 dose level. • If recurred, then dose reduce by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as ≥Grade 3 for more than 14 days despite temporary disruption of study drug.

Footnotes are on last table page.

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Table 9.g Dose Modification Guidelines for Nonhematologic Toxicity for Cohort A (MLN1117+TAK-659) (continued)

NCI CTCAE Grade	MLN1117 Dose Modification	TAK-659 Dose Modification
AST/ALT (continued)		
All other Grade 4 nonhematologic toxicities	Consider permanently discontinuing MLN1117 based on causality except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor project clinician or designee. If the patient is not withdrawn from the study, the MLN1117 dose will be reduced to at least 1 dose level lower when toxicity resolves to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2).	Consider permanently discontinuing TAK-659 based on causality except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor. If the patient is not withdrawn from the study, the TAK-659 dose will be reduced to at least 1 dose level lower when toxicity resolves to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2).

ALT=alanine aminotransferase, AST=aspartate aminotransferase, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, SOC=system organ class, ULN=upper limit of normal range.

9.4.4 Dose Modification Guidelines for Cohorts B, C, and D (MLN1117+Alisertib/Paclitaxel/Docetaxel)

9.4.4.1 Criteria for Beginning or Delaying a Treatment Cycle for Cohort B

Treatment with alisertib and MLN1117 in Cohort B will be repeated every 28 days. Both alisertib and MLN1117 will be administered following a 3-days-on and 4-days-off schedule for the first 3 weeks, and only MLN1117 will be administered in the fourth week of a given cycle. The patient must meet the following criteria before starting the next treatment cycle for Cohort B patients:

- ANC ≥1500/mm^3.
- Platelet count ≥100,000/mm^3.
- All toxicity considered to be related to treatment with MLN1117 or any of the combination partners must have resolved to ≤Grade 1, baseline values, or to a level considered acceptable by the investigator.
- There has been a minimal rest period of 10 days since last dose of alisertib.

If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for re-treatment have been met. If the patient continues to fail to meet the above-cited criteria, therapy should be delayed and re-evaluation continued. Should the start of the next cycle be delayed for ≥2 weeks because of incomplete recovery from treatment-related toxicity, the dose will be reduced by 1 dose level when therapy resumes. Should treatment be delayed for 3 weeks because of incomplete recovery from treatment-related toxicity, therapy with alisertib should be discontinued, or dose reduction by more than 1 dose level should be considered if, in the investigator's opinion, therapy still has a reasonable probability of providing a benefit.

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9.4.4.2 Retreatment Criteria for Paclitaxel or Docetaxel (Cohort C or D)

Per the prescribing information for paclitaxel and docetaxel, the patient must meet the following re-treatment criteria before starting the next dose of paclitaxel (Cohort C) or docetaxel (Cohort D):

- ANC $\geq 1500/mm^3$.
- Platelet count $\geq 100{,}000/mm^3$.
- Total bilirubin <ULN, or ALT and/or AST $\leq 1.5\times$ULN concomitant with alkaline phosphatase (ALP) $\leq 2.5\times$ULN (for docetaxel only).

For patients treated with docetaxel in combination with MLN1117, 1 dose of 75 mg/m^2 docetaxel is given per 21-day cycle. If a patient fails to meet the docetaxel retreatment criteria, the next cycle of docetaxel dosing should be delayed for 1 week while supportive care is given based on the local standard practice or as specified in Section 9.8.11. The patient should be re-evaluated after 1 week to determine whether the criteria for docetaxel retreatment have been met. If the criteria have not been met, further delay of the next cycle of docetaxel and re-evaluation of docetaxel retreatment criteria will occur at weekly intervals until all retreatment criteria are satisfied. Dose modification guidelines will be followed to determine whether the dose of docetaxel will be maintained or reduced when docetaxel dosing is resumed.

For patients treated with MLN1117+paclitaxel, 3 doses of 80 mg/m^2 paclitaxel will be given on Day 1, Day 8, and Day 15 in 28-day treatment cycles. If the patient fails to meet retreatment criteria for paclitaxel before Day 1 dosing in a given cycle, the start of the cycle will be delayed. If the retreatment criteria are not met for the Day 8 dosing of paclitaxel, the Day 8 dose will be delayed to Day 15 (provided that all retreatment criteria are met on Day 15), and the third dose will be withheld so that the cycle will not be further expanded beyond 28 days. If further delay is needed, the second and third doses of paclitaxel will be withheld, and paclitaxel will be resumed in the next cycle. If the retreatment criteria are not met for the Day 15 dosing of paclitaxel, this third dose of paclitaxel within a cycle will be withheld and paclitaxel will be resumed in the next cycle.

Discontinuation of study treatment should be considered if, because of lack of adequate recovery of the toxicities, there is a delay of a new cycle (due to Day 1 dosing delay for Cohort C or D) for ≥21 days (≥3 weeks), or a failure to resume the next cycle due to a delay of Day 8 or Day 15 paclitaxel dosing (for Cohort C only) for ≥21 days (≥3 weeks) after the initial delay. An exception may be considered in the case of investigator-determined clinical benefit and discussion with the sponsor project clinician (or designee). However, study treatment may be resumed only after these retreatment criteria are fully met. If a delay of ≥4 days (≥2 weeks) is required for resolution of toxicities before meeting the pretreatment criteria, dose reduction of paclitaxel and docetaxel to the next lower level should be considered (Table 9.e). The need for dose reductions below those stated in Table 9.e should result in withdrawal of the patient from the study.

If the toxicities that result in failure to meet the paclitaxel or docetaxel retreatment criteria are determined to be related to paclitaxel or docetaxel and not to MLN1117, patients should continue to receive MLN1117 according to the planned dose and regimen. If in the investigator's opinion, MLN1117 contributes to the toxicities (related or possibly related) that lead to not meeting

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paclitaxel or docetaxel retreatment criteria, dose delay or modification of MLN1117 should be considered per the dose modification guidelines in Section 9.4.4.3.

9.4.4.3 Dose Modification for Hematologic and Nonhematologic Toxicity: MLN1117 and Other Combination Agents (Alisertib/Paclitaxel/Docetaxel)

A decision regarding which study drug requires dose modification will be dependent upon the toxicity, its onset, and time course. The causal relationship of any reported events (AEs or SAEs) should be assessed by the investigator in relation to MLN1117 and in relation to the combination agent (alisertib, paclitaxel, or docetaxel) in Cohort B, C, or D. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines and the causal relationship to 1 or both study drugs. Guidelines for dose modifications for hematologic and nonhematologic toxicity are presented in Table 9.h and Table 9.i, respectively. In particular, since the docetaxel retreatment criteria include specific requirements pertaining to liver function tests, dose modification guidance for hepatotoxicity is provided specifically for Cohort D in Table 9.j. After discussion between the investigator and the sponsor project clinician, alternative dose modifications may be recommended to maximize exposure of study treatment while protecting patient safety.

Table 9.h Dose Modification Guidelines for Hematologic Toxicities for Cohort B (MLN1117+Alisertib), Cohort C (MLN1117+Paclitaxel), and Cohort D (MLN1117+Docetaxel)

NCI CTCAE Grade	Description	Dose Modification for MLN1117	Dose Modification for Combination Agent (a)
Neutropenia			
2 or 3	ANC <1500 to 500/mm^3; <1.5 to 0.5×10^9/L	No change. Continue MLN1117 at same dose and schedule.	Hold combination agent until ANC ≥1500/mm^3, then restart at the same dose.
4	ANC <500/mm^3; <0.5×10^9/L	Hold MLN1117 until ANC ≥1500/mm^3, then restart MLN1117 at same dose and schedule. In case of repeat occurrence at a reduced dose of the combination agent, MLN1117 or both may be reduced by 1 level.	Hold combination agent until ANC ≥1500/mm^3, then restart combination agent. If resolved in ≤7 days, maintain the same dose of combination agent. If resolved in >7 days, reduce dose by 1 level.

Footnotes are on last table page.

Table 9.h Dose Modification Guidelines for Hematologic Toxicities for Cohort B (MLN1117+Alisertib), Cohort C (MLN1117+Paclitaxel), and Cohort D (MLN1117+Docetaxel) (continued)

NCI CTCAE Grade	Description	Dose Modification for MLN1117	Dose Modification for Combination Agent (a)
Neutropenia (continued)			
Other	Febrile Neutropenia ANC <1000/mm^3 and fever defined as a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour); OR ANC <1000/mm^3 with systemic infection	Hold MLN1117 until ANC ≥1500/mm^3 and both fever and infection are resolved, then restart MLN1117 at same dose and schedule. In case of repeat occurrence at a reduced dose of the combination agent, MLN1117 may be reduced by 1 level.	Hold combination agent until ANC ≥1500/mm^3 and both fever and infection are resolved, then restart combination agent at reduced dose by 1 level.
Thrombocytopenia			
1 or 2	PLT 50,000 to 100,000/mm^3; <50 to 100×10^9/L	No change. Continue MLN1117 at same dose and schedule.	Hold combination agent until PLT ≥100,000/mm^3, then restart combination agent at the same dose.
3	PLT 25,000 to 500,000/mm^3; <25 to 50×10^9/L	Hold MLN1117 until PLT ≥100,000/mm^3 or baseline; restart MLN1117 at same dose and schedule.	Hold combination agent until PLT ≥100,000/mm^3. If resolved in ≤7 days, maintain the same dose of combination agent. If resolved in >7 days, reduce dose by 1 level. Please see Table 9.e.
4	PLT <25,000/mm^3; <25×10^9/L	Hold MLN1117 until PLT ≥100,000/mm^3 or baseline; restart MLN1117 at same dose. In case of recurrence at a reduced dose of the combination agent, MLN1117 may be reduced by 1 level.	Hold combination agent until PLT ≥100,000/mm^3 or baseline. When resolved, reduce dose by 1 level.

Footnotes are on last table page.

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Table 9.h Dose Modification Guidelines for Hematologic Toxicities for Cohort B (MLN1117+Alisertib), Cohort C (MLN1117+Paclitaxel), and Cohort D (MLN1117+Docetaxel) (continued)

NCI CTCAE Grade	Description	Dose Modification for MLN1117	Dose Modification for Combination Agent (a)
Thrombocytopenia (continued)			
Other	PLT <10,000 cells/mm^3; OR clinically significant bleeding	Consider permanently discontinuing MLN1117, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor. If the patient is not withdrawn from the study, the MLN1117 dose will be reduced to at least 1 dose level lower when PLT ≥100,000/mm^3 and/or clinically significant bleeding are completely resolved. See Table 9.e for dose modification guidelines.	Consider permanently discontinuing the combination agent, except when the investigator determines that the patient is obtaining a clinical benefit and the investigator has discussed this with the sponsor. If the combination agent is not discontinued, then the combination agent dose will be reduced to at least 1 dose level lower when PLT ≥100,000/mm^3 and/or clinically significant bleeding are completely resolved.
Anemia			
3	Hgb <8.0 g/dL not due to bleeding; transfusion indicated	Hold MLN1117 until Hgb ≥9.0 g/dL or baseline; restart MLN1117 at same dose. In case of repeat occurrence at a reduced dose of the combination agent, MLN1117 may be reduced by 1 level.	Hold combination agent until Hgb ≥9.0 g/dL. If resolved in ≤7 days, maintain the same dose of combination agent. If resolved in >7 days, reduce dose by 1 level.
4	Life-threatening consequences; urgent intervention indicated	Hold MLN1117 until Hgb ≥9.0 g/dL or baseline; restart MLN1117 at same dose with a reduced dose of combination agent or at a reduced dose by at least 1 level or consider discontinuation.	Hold combination agent until Hgb ≥9.0 g/dL. When resolved, reduce dose by at least 1 level or consider discontinuation.

ANC=absolute neutrophil count, Hgb=hemoglobin, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, PLT=platelets.
(a) Combination agent is alisertib (Cohort B), paclitaxel (Cohort C), or docetaxel (Cohort D).

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Table 9.i Dose Modification Guidelines for Nonhematologic Toxicity for Cohort B (MLN1117+Alisertib), Cohort C (MLN1117+Paclitaxel), and Cohort D (MLN1117+Docetaxel)

NCI CTCAE Grade	MLN1117 Dose Modification	Combination agent dose modification (a)
Hyperglycemia		
Grade 2 (Fasting glucose value >160 to 250 mg/dL; fasting glucose value >8.9 to 13.9 mmol/L)	Continue MLN1117 at same dose and schedule. Refer to Section 9.8.2 for guidelines on hyperglycemia management.	Continue combination agent at same dose and schedule. Refer to Section 9.8.2 for guidelines on hyperglycemia management.
Grade 3 (>250 to 500 mg/dL; >13.9 to 27.8 mmol/L; hospitalization indicated)	Hold MLN1117 until hyperglycemia ≤Grade 2. Optimize antihyperglycemic therapy and resume MLN1117 based on timing of recovery. • ≤1 week: resume MLN1117 at same dose and schedule. • >1 but ≤2 weeks or recurrent with antihyperglycemic treatment: reduce MLN117 dose to the next lower dose level for all subsequent cycles. • >2 weeks: stop MLN1117 and withdraw subject from study.	Continue combination agent at same dose and schedule.
Grade 4 (>500 mg/dL; >27.8 mmol/L; life-threatening consequences)	Hold MLN1117 until hyperglycemia ≤Grade 2. • ≤1 week: reduce MLN117 dose to the next lower dose level for all subsequent cycles. • >1 week: discontinue.	Hold combination agent until hyperglycemia ≤Grade 2. Continue combination agent at same dose and schedule.

Footnotes are on last table page.

Table 9.i Dose Modification Guidelines for Nonhematologic Toxicity for Cohort B (MLN1117+Alisertib), Cohort C (MLN1117+Paclitaxel), and Cohort D (MLN1117+Docetaxel) (continued)

NCI CTCAE Grade	MLN1117 Dose Modification	Combination agent dose modification (a)
AST/ALT (b)		
Grade 3 elevation of single enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 2)	Maintain the dose of MLN1117 with close monitoring.	Maintain the dose of the combination agent with close monitoring.
Grade 3 elevation of both AST and ALT	Hold MLN1117 until AST and ALT return to Grade 1. Restart MLN1117 at the same dose if resolved within 7 days or reduce by 1 level if resolution is more than 7 days. If concomitant bilirubin elevation >Grade 1 is attributable to drug toxicity, discontinue treatment.	Hold combination agent until AST and ALT return to Grade 1. Restart the combination agent at the same dose if resolved within 7 days or reduce by 1 level if resolution is more than 7 days. If concomitant bilirubin elevation >Grade 1 is attributable to drug toxicity, discontinue treatment.
Grade 4 elevation of AST and/or ALT	Hold MLN1117 until AST and ALT return to Grade 1. Restart MLN1117 at a reduced dose by 1 level. If concomitant bilirubin elevation >Grade 1 is attributable to drug toxicity, discontinue treatment.	Hold the combination agent until AST and ALT <2.5×ULN. Restart combination agent at a reduced dose by 1 level. If concomitant bilirubin elevation >Grade 1 is attributable to drug toxicity, discontinue treatment.
Stomatitis		
Grade 2	Maintain MLN1117 if tolerated by the patient. Hold MLN1117 if not tolerated by the patient until recovery to ≤Grade 1, then restart at same dose.	Maintain combination agent if tolerated by the patient. Hold combination agent if not tolerated by the patient until recovery to ≤Grade 1, then restart at same dose.
Grade 3	Hold MLN1117 if not tolerated by the patient until recovery to ≤Grade 1, then restart at same dose. If after dose delay of the combination agent and provision of standard care for 7 days, the stomatitis has not resolved, dose reduction of MLN1117 should be considered, initially by 1 dose level.	Hold combination agent until recovery to ≤Grade 1, then restart at a dose reduced by 1 level.
Grade 4	Discontinue MLN1117 and withdraw patient from the study.	Discontinue combination agent and withdraw patient from the study.

Footnotes are on last table page.

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Table 9.i Dose Modification Guidelines for Nonhematologic Toxicity for Cohort B (MLN1117+Alisertib), Cohort C (MLN1117+Paclitaxel), and Cohort D (MLN1117+Docetaxel) (continued)

NCI CTCAE Grade	MLN1117 Dose Modification	Combination agent dose modification (a)
Other Nonhematologic Toxicities		
Peripheral neuropathy ≥Grade 3	Maintain the same dose/regimen of MLN1117 if determined to be unrelated.	Permanently discontinue combination agent.
<u>All other ≥Grade 3 nonhematologic toxicities with the exception of:</u> • Grade 3 nausea, vomiting, and diarrhea resolved to ≤Grade 1 or baseline within 1 week with optimal antiemetics and antidiarrheals following standard of care • Transient Grade 3 fatigue (lasting <1 week) • Grade 3 rash lasting ≤7 days with optimal treatment • Any other Grade 3 nonhematologic toxicity that can be controlled to ≤Grade 1 or baseline in 1 week with appropriate treatment in 7 days	Hold MLN117 if determined to be related to MLN1117 until resolution to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2): • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then reduce dose by 1 dose level. • If recurs, then reduce dose by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as ≥Grade 3 for more than 14 days despite temporary disruption of study drug.	Hold combination agent if determined to be related to docetaxel until resolution to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2): • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then dose reduce by 1 dose level. • If recurs, then reduce dose by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as ≥Grade 3 for more than 14 days despite temporary disruption of study drug.

Footnotes are on last table page.

[redacted]

Table 9.i Dose Modification Guidelines for Nonhematologic Toxicity for Cohort B (MLN1117+Alisertib), Cohort C (MLN1117+Paclitaxel), and Cohort D (MLN1117+Docetaxel) (continued)

NCI CTCAE Grade	MLN1117 Dose Modification	Combination agent dose modification (a)
All other Grade 4 nonhematologic toxicities	Consider permanently discontinuing MLN1117 based on causality, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor. If the patient's treatment is not discontinued, the MLN1117 dose will be reduced to at least 1 dose level lower when toxicity resolves to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2).	Consider permanently discontinuing combination agent based on causality, except when the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient's treatment is not discontinued, the combination agent dose will be reduced to at least 1 dose level lower when toxicity resolves to ≤Grade 1, baseline, or a level acceptable by the investigator (must be ≤Grade 2).

ALT=alanine aminotransferase, AST=aspartate aminotransferase, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, ULN=upper limit of normal range.
(a) Combination agent is alisertib (Cohort B), paclitaxel (Cohort C), or docetaxel (Cohort D).
(b) For Cohorts B and C only; please refer to Table 9.j for Cohort D.

Dose modification guidelines for managing abnormal liver function tests (LFTs) or hepatotoxicity are provided in Table 9.j for Cohort D, in concert with the docetaxel retreatment criteria per docetaxel label.

[redacted]

Table 9.j Dose Modification Guidelines for Abnormal Liver Function Tests or Hepatotoxicity for Cohort D (MLN1117+Docetaxel)

NCI CTCAE Grade	Description	Dose Modifications for MLN1117	Dose Modifications for Docetaxel
	ALT and/or AST >2.5 to 5×ULN and ALP ≤2.5×ULN, or AST/ALT >1.5 to ≤5×ULN and ALP >2.5 to ≤5×ULN	• When ALP >2.5×ULN together with bilirubin <ULN, hold MLN1117 until both ALT and AST ≤1.5×ULN • When ALP <2.5×ULN together with bilirubin <ULN, hold MLN1117 until both ALT and AST <2.5×ULN. Then resume study drug at the same dose and schedule.	Reduce docetaxel by 1 dose level for the next cycle.
	ALT and/or AST and/or ALP >5 to ≤20×ULN	• When ALP >2.5×ULN together with bilirubin <ULN, hold MLN1117 until both ALT and AST ≤1.5×ULN • When ALP <2.5×ULN together with bilirubin <ULN, hold MLN1117 until both ALT and AST <2.5×ULN. If resolved <7 days, resume study drug at the same dose and schedule. If resolved >7 days, reduce study drug by 1 dose level (first occurrence) and by 2 dose levels (repeat occurrence). Discontinue if bilirubin >Grade 1.	Discontinue docetaxel permanently.
4	ALT and/or AST >20×ULN	• When ALP >2.5×ULN together with bilirubin <ULN, hold MLN1117 until both ALT and AST ≤1.5×ULN; OR • When ALP <2.5×ULN together with bilirubin <ULN, hold MLN1117 until both ALT and AST <2.5×ULN. When resolved, reduce study drug by 2 dose levels. Discontinue if bilirubin >Grade 1.	Discontinue docetaxel permanently.

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, ULN=upper limit of the normal range.

9.5 Excluded Concomitant Medications and Procedures

Medications and procedures in the following subsections are prohibited during the study.

9.5.1 Excluded Concomitant Medications Applicable to All Cohorts (Cohorts A-D)

- Use of other investigational medicinal products or devices.

[redacted]

- Other antineoplastic therapy, including chemotherapy, immunotherapy, targeted agents, and radiation or surgery (patients can have palliative radiation or surgery during the study for pre-existing lesions upon discussion with the sponsor project clinician).
- Daily, chronic, or regular use of any proton pump inhibitors (such as omeprazole, esomeprazole, lansoprazole, pantoprazole) is prohibited in all cohorts. Patients may be given alternative agents to manage gastric acidity or reflux (eg, histamine-2 [H_2]-receptor antagonists or antacids) according to the guidelines described in Section 9.6.2.
- Strong inhibitors/inducers of CYP3A are prohibited in all cohorts. Examples of strong CYP3A inhibitors/inducers are provided in Appendix F.

9.5.2 Excluded Concomitant Medications Applicable to a Specific Cohort

- Cohort A (MLN1117+TAK-659): Inhibitors/inducers of P-gp are prohibited. Examples of P-gp inhibitors/inducers are provided in Appendix G.
- Cohort B (MLN1117+alisertib): Although not prohibited, the use of benzodiazepines for the prophylaxis or treatment of nausea or vomiting is discouraged because of the potential benzodiazepine-like effects of alisertib.
- Cohort C (MLN1117+paclitaxel): Please refer to the most recent paclitaxel USPI or SmPC for information on medications that are prohibited in patients receiving paclitaxel.
- Cohort D (MLN1117+docetaxel): Please refer to the most recent docetaxel USPI or SmPC for information on medications that are prohibited in patients receiving docetaxel.

9.6 Permitted Concomitant Medications and Procedures

9.6.1 Paclitaxel or Docetaxel Premedication for Cohorts C or D

Premedication before and/or concomitant with paclitaxel or docetaxel, including corticosteroids and antiemetics, will be administered in accordance with the recommendations in the paclitaxel (Cohort C) or docetaxel (Cohort D) prescribing information. Appropriate institutional practices consistent with paclitaxel or docetaxel label and recommendation should be followed.

All patients receiving docetaxel should be premedicated with corticosteroids to reduce the incidence and severity of fluid retention and/or hypersensitivity reaction. For example, dexamethasone 16 mg per day (eg, 8 mg BID) may be used for 3 days starting 1 day before docetaxel when docetaxel is administered every 3 weeks. When paclitaxel is administered weekly, premedication to prevent paclitaxel-associated hypersensitivity reactions may include corticosteroid (eg, high-dose dexamethasone as a 20-mg single dose administered 6 to 12 hours before paclitaxel treatment, which can be reduced with subsequent paclitaxel cycles), diphenhydramine, and an H_2-receptor antagonist (eg, cimetidine or ranitidine). Only brief administration of a H_2-receptor antagonist (eg, single dose of cimetidine or ranitidine) is allowed if required on the day of paclitaxel administration, but prolonged administration of a H_2-receptor

antagonist (or any other agents that can alter stomach pH or drug absorption) is to be avoided (see Section 9.5).

Other premedications including, but not limited to, 5-hydroxytryptamine ($5\text{-}HT_3$) antiemetics may be administered per the local standard of care on the day of paclitaxel or docetaxel administration.

9.6.2 Histamine-2 Receptor Antagonists and Neutralizing Antacids

- Restricted use of H_2-receptor antagonists (such as ranitidine, famotidine, cimetidine, and nizatidine) is permitted during the treatment cycle days listed by cohort below. However, the timing after the previous MLN1117 dose (6 hours) or before the next MLN1117 dose (24 hours) must be strictly followed.
  - Cohort A (MLN1117+TAK-659) and Cohort B (MLN1117+alisertib): Treatment with an H_2-receptor antagonist is permitted if it is administered at least 6 hours after administration of MLN1117 and 24 hours before the next scheduled dose of MLN1117. Patients are thus allowed to take an H_2-receptor antagonist on Days 4, 5, 6, 7, 11, 12, 13, 14, 18, 19, 20, 21, 25, 26, 27, and 28 of each cycle.
  - Cohort C (MLN1117+paclitaxel): Treatment with an H_2-receptor antagonist is permitted if it is administered at least 6 hours after administration of MLN1117 and 24 hours before the next scheduled dose of MLN1117. Treatment with an H_2-receptor antagonist is allowed on Days 1, 8, and 15 if required to prevent hypersensitivity reactions associated with paclitaxel administration. Should treatment with an H_2-receptor antagonist be warranted for paclitaxel premedication, the timing of MLN1117 administration must be adjusted accordingly on Days 2, 9, and 16. Patients are also allowed to take an H_2-receptor antagonist on Days 5, 6, 7, 12, 13, 14, 19, 20, 21, 26, 27, and 28 of each cycle.
  - Cohort D (MLN1117+docetaxel): Treatment with an H_2-receptor antagonist is permitted if it is administered at least 6 hours after administration of MLN1117 and 24 hours before the next scheduled dose of MLN1117. Treatment with an H_2-receptor antagonist is allowed on Day 1 if required to prevent hypersensitivity reactions associated with docetaxel administration. Should treatment with an H_2-receptor antagonist be warranted for docetaxel premedication, the timing of MLN1117 administration must be adjusted accordingly on Day 2. Patients are also allowed to take an H_2-receptor antagonist on Days 5, 6, 7, 8, 12, 13, 14, 15, 19, 20, and 21 of each cycle.
- Neutralizing antacids, such as Maalox Max (magnesium and aluminum hydroxide) and Tums (calcium carbonate), antigas preparations, and calcium supplements are not permitted from 2 hours before and within 6 hours after study drug administration on MLN1117 dosing days, and as needed on non-dosing days.

9.6.3 Additional Concomitant Medications and Procedures

- Oral contraceptive agents or any other type of hormonal contraception are permitted.

[redacted]

- Additional concomitant medications and procedures are permitted during the course of the study (please refer to Section 9.6) to prevent and/or actively manage AEs related or not related to the study drug(s) unless prohibited (Section 9.5) as specified in the protocol.

9.7 Precautions and Restrictions

Patients who show evidence of hyperglycemia during the study should be encouraged to follow a low carbohydrate diet, limit alcohol intake, and increase physical activity and exercise. No dietary restriction is required other than avoiding food or beverages containing grapefruit or juice from the grapefruit within 7 days before the first dose of study drug treatment and throughout the study (see Section 9.5).

It is not known what effects MLN1117 has on human pregnancy, mother's milk, or development of the embryo or fetus when administered in combination with TAK-659, alisertib, paclitaxel, or docetaxel. Therefore, female patients participating in this study should avoid becoming pregnant, breastfeeding a baby, or donating eggs (ova) while on this study and for 30 days (180 days for TAK-659), or longer for docetaxel and paclitaxel as mandated by local labeling, after receiving their last dose of study drug. Male patients should avoid impregnating a female partner or donating sperm while on this study and for 120 days (180 days for TAK-659), or longer for docetaxel and paclitaxel as mandated by local labeling, after receiving their last dose of study drug. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method (see Appendix E) and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form through 30 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days), or for as long as mandated by local labeling for docetaxel and paclitaxel, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form through 30 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days), or for as long as mandated by local labeling for docetaxel and paclitaxel. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

[redacted]

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

- Practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days), or for as long as mandated by local labeling for docetaxel and paclitaxel, OR
- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, during the entire study treatment period and through 120 days after the last dose of study drug (with the exception of those subjects assigned to TAK-659, for whom the duration required is 180 days), or for as long as mandated by local labeling for docetaxel and paclitaxel. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

9.8 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded.

Supportive care agents, such as blood products, antiemetics, and pain medications are permitted as needed per American Society of Oncology (ASCO) guidelines or local institutional practices. However, these agents should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation.

9.8.1 Hematologic Events

A complete blood count (CBC) should be monitored regularly as outlined in the Schedules of Events (SOEs) (Appendix A) for each cohort with additional testing obtained according to standard clinical practice. Transfusion of blood products (such as packed red blood cell [RBC] and platelets) and use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF] or granulocyte macrophage colony stimulating factor [GM-CSF]) are permitted as necessary and per local institutional practice or ASCO guidelines. In general, RBC transfusion is recommended for all symptomatic patients with anemia or any asymptomatic patients with a hemoglobin <8 g/dL with the purpose of maintaining the hemoglobin between 8 and 10 g/dL. Platelet transfusion should be given prophylactically to patients with platelet counts <10,000 cells/mm^3 or to any patients with signs of overt bleeding, such as oral purpura. Each transfusion episode, including the type of transfusion (RBC and/or platelet), should be recorded.

9.8.2 Hyperglycemia

Hyperglycemia or elevated fasting blood glucose levels have been observed following MLN1117 administration. It may be noted that patients in Cohorts C and D will be more prone to developing hyperglycemia due to premedication with corticosteroids in order to prevent hypersensitivity and/or other reactions associated with paclitaxel or docetaxel administration.

[redacted]

All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff. It is not necessary to treat patients with transient Grade 1 or 2 hyperglycemia. It is important to check if blood glucose levels return to normal values during the off-drug days in patients with hyperglycemia on days of MLN1117 administration. Metformin is the first-line drug of choice for sustained Grade 1, Grade 2, and asymptomatic Grade 3 hyperglycemia. Metformin does not cause hypoglycemia which is important to take into account as MLN1117 is administered with a 3-day-on 4-day-off schedule, and there is potential for variations in glycemic values between on-treatment and off-treatment days. The investigator may choose to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting glucose level above the ULN but ≤160 mg/dL) or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with ≥Grade 2 hyperglycemia (fasting glucose >160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. Metformin is contraindicated in patients with risk factors for lactic acidosis (glomerular filtration rate <60 mL/minute, liver impairment, sepsis). Patients can be initially treated with metformin at 500 mg PO QD and titration up to a maximum of 1000 mg PO BID as needed. Concurrent DPP-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered in addition to metformin. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution due to the higher risk of inducing hypoglycemia in patients. The investigator should consult an endocrinologist, if needed, to aid in optimizing the patient's hyperglycemia treatment plan.

All patients developing hyperglycemia during the study should be encouraged to adopt lifestyle modifications, such as balanced diet including limited consumption of carbohydrates and alcohol, and increased physical activity and exercise. Table 9.k summarizes the guidance for management of and study drug dose modification for patients with hyperglycemia.

[redacted]

Table 9.k Management of Hyperglycemia

Grade	Description	Treatment	MLN1117 Dose Modifications (a)
1	Fasting blood sugar >ULN to 160 mg/dL	• Start once-per-day home glucose monitoring. • Therapeutic lifestyle changes (TLC). • Consider initiation of oral hypoglycemic agent.	None
2	>160 to 250 mg/dL	• Start twice-per-day home glucose monitoring. • TLC • Initiate metformin and/or insulin if not well controlled on oral agent. Add basal insulin if not controlled after 1 week.	None
≥3	>250 mg/dL	• Start home glucose monitoring before breakfast and dinner. • TLC • Initiate metformin with rapid titration and/or insulin. • If symptomatic and/or hypovolemic, consider hospital admission for intravenous fluids, diabetic consultation, and 4-injection basal bolus insulin injection.	Hold MLN1117 until ≤Grade 2. Resume study drug based on timing of recovery after maximal treatment: • ≤1 week: resume study drug at same dose and schedule. • >1 but ≤2 weeks: reduce study drug by 1 dose level • >2 but ≤3 weeks: reduce study drug by 2 dose levels. • >3 weeks: withdraw patient from the study. • Please see Table 9.e for dose modification guidelines.

Prevention/Prophylaxis:

- Follow fasting glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Fasting blood glucose levels ≥160 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.
- Most episodes of Grade 1 to 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy at the lowest therapeutic dose is recommended to prevent higher grade hyperglycemia.
- Therapeutic lifestyle changes: a low carbohydrate diet, limited alcohol consumption, increased physical activity.

HbA1c=glycosylated hemoglobin, ULN=upper limit of the normal range.
(a) For additional details, please refer to Table 9.e.

[redacted]

9.8.3 Nausea and Vomiting

This study allows prophylactic use of antiemetic and antinausea medications as clinically indicated according to the institutional standard of care. These may be administered before each dose of the study drugs as needed throughout the study, except before Cycle 1 Day 1 of Part 1 (dose escalation) when prophylactic antiemetics can be used only after nausea and vomiting have been observed. In addition, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. An optimal antiemetic regimen is defined as one that employs both a 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules.

9.8.4 Diarrhea

Prophylactic antidiarrheals will not be used in this study; however, patients should be instructed to take loperamide or comparable antidiarrheal medication according to institutional or local practice, once infectious causes are ruled out. Adequate fluid intake should be maintained to avoid dehydration, and any fluid deficit should be corrected before initiation of treatment with study drugs and during treatment.

9.8.5 Stomatitis/Oral Mucositis

Pooled data across the alisertib single-agent studies reported stomatitis (31%) as 1 of the most common TEAEs. Oral mucositis is also 1 of the common AEs observed in patients treated with paclitaxel or docetaxel. Please refer to the most recent paclitaxel or docetaxel USPI or SmPC for more information for the management of oral mucositis. Guidance for the management of patients who develop oral mucositis is provided in Table 9.i. Prevention or prophylaxis of oral mucositis may include initiation of a nonalcoholic mouthwash or 0.9% salt water rinses 4 to 6 times daily with start of therapy before signs of mucositis develop. Mouth washes or rinses may be used to treat patients with Grade 1 oral mucositis, and topical steroids may be considered with observation of the earliest signs of mucositis. Patients with ≥Grade 2 oral mucositis may be treated with topical analgesic mouth treatments, topical corticosteroids, and antiviral or antifungal therapy if indicated. Intralesional corticosteroids may be considered for Grades 3 and 4 lesions. Agents containing hydrogen peroxide, iodine, and thyme derivatives should be avoided in the management of patients with oral mucositis as these agents may worsen mouth ulcers.

9.8.6 Rash

Prophylactic measures should be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of ≤Grade 2 rash, treatment with a topical steroid cream/ointment and/or oral antihistamines or antibiotics may be considered. Patients with rash ≥Grade 3 should be managed aggressively (topical steroid cream/ointment, oral antihistamines, oral antibiotics, and/or pulsed corticosteroids). The investigator should consider consulting a dermatologist or other specialist if needed. A skin biopsy at the site of the rash is highly recommended to ascertain the etiology and histology of the rash. Refer to Table 9.g and Table 9.i for dose modification guidelines.

[redacted]

9.8.7 Asthenia, Weakness, and Fatigue

The management of patients with asthenia, weakness, and fatigue includes initiation of appropriate medical therapy and monitoring. If Grade 1 or Grade 2 toxicity is tolerated by the patient, then no adjustment of study drugs (MLN1117 in combination with TAK-659, alisertib, paclitaxel, or docetaxel) is required. If study drugs are to be held, then both agents should be held for the patient in that combination drug cohort. If Grade 2 toxicity is not tolerated by the patient, hold study drugs until recovery to ≤Grade 1, then reinitiate at same dose. For ≥Grade 3 toxicity, hold study drugs until recovery to ≤Grade 1. Reinitiate study drug(s) at a reduced dose by 1 level (first occurrence) and by 2 levels (repeat occurrence). Please refer to Table 9.e for dose level guidelines.

9.8.8 Elevated Serum Lipase (Cohort A)

Elevated levels of serum lipase, without any clinical symptoms, have been reported in patients treated with TAK-659. Dose modification will not be required for any Grade 1 or 2 elevation of serum lipase (≤2.0×ULN). Dose modifications will be considered in accordance with Table 9.g and in consultation with the investigator and sponsor clinician (or designee), if there is Grade 3 or 4 elevation of serum lipase (>2.0×ULN) or if any elevated serum lipase is also presented with related clinical symptoms.

9.8.9 Central Nervous System Effects (Cohort B)

Alisertib-treated patients may experience excessive sedation. If sedation is 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. Dose modifications will also be considered in accordance with Table 9.i and in consultation with the investigator and sponsor project clinician (or designee).

9.8.10 Paclitaxel-Related Clinical Events (Cohort C)

Please refer to the most recent paclitaxel USPI or SmPC for more information on paclitaxel-related clinical events, such as conduction abnormalities, hypertension, peripheral neuropathy, etc; and for the management of clinical events in patients receiving paclitaxel.

9.8.11 Docetaxel-Related Clinical Events (Cohort D)

Please refer to the most recent docetaxel USPI or SmPC for more information on docetaxel-related clinical events, such as fluid retention, cystoid macular edema, peripheral neuropathy, etc; and for the management of clinical events in patients receiving docetaxel.

9.9 Blinding and Unblinding

This is an open-label study.

[redacted]

9.10 Description of Investigational Agents

9.10.1 MLN1117

MLN1117 will be supplied as tablets for PO administration, and will be available in the following 2 dose strengths:

- MLN1117 100 mg tablets.
- MLN1117 300 mg tablets.

MLN1117 tablets have been developed as an immediate-release formulation for PO administration. The drug product formulation consists of a mixture of MLN1117, microcrystalline cellulose, low substituted hydroxypropyl cellulose, sodium croscarmellose, colloidal silicon dioxide, and magnesium stearate.

9.10.2 TAK-659

TAK-659 has been formulated into immediate-release film-coated tablets for use in clinical studies via a common granulation process. Three different tablet dosage strengths, 20, 60, and 100 mg, were formulated. The formulation contains compendial excipients that include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. Tablets were coated with Opadry film coat.

9.10.3 Alisertib

An enteric-coated tablet (ECT) dosage form of alisertib has been developed for use in clinical studies. One ECT dosage strength, 10 mg, expressed as alisertib free acid, has been formulated. The key formulation excipients that aid in the in vivo absorption of the drug are the buffer (sodium bicarbonate), the surfactant (sodium lauryl sulfate), and the enteric coating. The other formulation excipients such as binder (povidone), filler (microcrystalline cellulose), disintegrant (croscarmellose sodium), and lubricant (sodium stearyl fumarate) serve as manufacturing aids. Refer to the IB for full details.

9.10.4 Paclitaxel and Docetaxel

Docetaxel and paclitaxel both are commercially available drugs administered IV.

Please refer to the current version of the MLN1117, TAK-659, and alisertib IBs, and the USPI or SmPC for docetaxel and paclitaxel for full details.

9.11 Preparation, Reconstitution, and Dispensation

MLN1117, TAK-659, alisertib, paclitaxel, and docetaxel are anticancer drugs, and as with other potentially toxic compounds, caution should be exercised when handling these drugs.

[redacted]

9.11.1 MLN1117

MLN117 will be provided in 14-count 30-cc high-density polypropylene (HDPE), with child-resistant caps and induction seals. MLN1117 bottles are to be dispensed according to the site procedures, and according to instruction and guidelines provided in the study Pharmacy Manual, including the requirement that tablets are stored in their original containers. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

9.11.2 TAK-659

Detailed instructions for the dispensing of TAK-659 immediate-release film-coated tablets are provided in the Pharmacy Manual. TAK-659 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-659.

9.11.3 Alisertib

The study drug alisertib will be provided by Takeda. Alisertib ECTs are packaged (10 tablets per bottle) in a 60-cc, 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.

9.11.4 Paclitaxel and Docetaxel

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

9.12 Packaging and Labeling

9.12.1 MLN1117

MLN1117 will be handled at the investigative site as open-label material. MLN1117 tablets will be provided in 14-count, 30-cc HDPE bottles, with child-resistant caps and induction seal. For both dose strengths, each bottle contains 14 tablets and will have a label containing pertinent study information, country-specific requirements, and a caution statement.

9.12.2 TAK-659

TAK-659 in 20-, 60- and 100-mg tablets will be packaged into round, white, HDPE bottles with induction seal, desiccant pack, and polypropylene child-resistant caps. Each bottle of TAK-659 will be labeled with either a single-panel or multilanguage label containing pertinent study information, country-specific requirements, and a caution statement.

9.12.3 Alisertib

The packaged and labeled study drug, alisertib, will be provided by the sponsor 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 ECTs are packaged into each 60-cc, HDPE bottle. Alisertib will be supplied as ECTs in 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.

9.12.4 Paclitaxel and Docetaxel

Docetaxel and/or paclitaxel may be supplied either by the study site from commercial sources (US sites) or provided by the sponsor (ex-US sites). When provided by the sponsor, docetaxel and paclitaxel will be appropriately labeled in compliance with local and regional regulations.

9.13 Storage, Handling, and Accountability

9.13.1 MLN1117

Upon receipt at the investigative site, MLN1117 study drug should be stored in the original bottles at room temperature from 15°C to 30°C (59°F to 86°F) until use. All temperature excursions will be reported to the sponsor 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 MLN1117 should be used before the retest date.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the subjects, will be provided and kept at the study site. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

Because MLN1117 is an investigational agent, it should be handled with due care. Patients will receive instructions for home storage and administration of MLN1117. Patients will receive diary cards to record dosing compliance of MLN1117.

Patients will be instructed to return any unused study drug in the original packaging along with their completed diary cards at the appropriate visits.

9.13.2 TAK-659

TAK-659 tablets should be stored in the original dispensing bottles. The container should be stored at the investigative site at controlled room temperature (20°C to 25°C; 68°F to 77°F; excursions permitted from 15°C to 30°C; 59°F to 86°F) and used before the retest date indicated on the label or accompanying documentation. Drug supply must be kept in an appropriate, limited access, secure place until it is dispensed to the enrolled patients, returned to sponsor, or forwarded to the sponsor's designee for destruction. Drug supplies received at the clinical sites will be counted and reconciled before being returned to the sponsor.

9.13.3 Alisertib

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

Because this 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 clean-up operation.

The product may be harmful by inhalation, ingestion, or skin absorption. 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 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.

9.13.4 Paclitaxel and Docetaxel

Docetaxel and paclitaxel should be stored according to the label and the instructions provided in the manufacturer's most recent USPI or SmPC.

Please refer to the site Pharmacy Manual for additional instructions regarding study drugs.

9.14 Other Protocol-Specified Materials

Not applicable.

[redacted]

10.0 STUDY CONDUCT

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

10.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central and secondary laboratories, the coordinating investigator for each member state/country, the interactive web response system (IWRS) provider, and the Quintiles team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

10.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC).

10.3 Treatment Group Assignments

In Part 1 (dose escalation) of the study, patients will be assigned to a current, open cohort. Refer to the Cohort Management Plan for detailed information on slot allocation in Part 1. Refer to Section 14.1.2 for a description of assignment to study drug treatment in Part 2 (see also Figure 7.a).

10.4 Study Procedures

Refer to the SOEs (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

10.4.1 Informed Consent

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

10.4.2 Enrollment

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

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

10.4.3 Patient Demographics

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

10.4.4 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 10.4.10.

10.4.5 Physical Examination

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

10.4.6 Patient Height

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

10.4.7 Vital Signs

Vital signs include blood pressure, heart rate, and temperature, to be determined at the times specified in the Schedule of Events (Appendix A).

10.4.8 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed at the times specified in the Schedule of Events (Appendix A).

10.4.9 Electrocardiogram

A 12-lead ECG will be administered at the time points specified in the SOEs (Appendix A).

10.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the electronic case report form (eCRF) from the date of the first dose of study drug through 30 days after the last dose of study drug. See Section 9.5 and Section 9.6 for a list of medications and therapies that are prohibited and/or allowed during the study.

10.4.11 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOEs (Appendix A). Refer to Section 11.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

10.4.12 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on Cycle 1 Day 1 with negative results available

before the first dose may be administered. A serum pregnancy test may also be performed within 3 days of dosing in place of the Cycle 1 Day 1 urine test.

10.4.13 Clinical Laboratory Evaluations

All scheduled clinical laboratory evaluations will be performed centrally. Additionally, the following safety laboratory tests should be performed locally for dosing decisions: standard hematology (with white blood cell differential count), AST, ALT, total bilirubin, ALP, creatinine, and fasting serum glucose. For patients allocated to Cohort A (TAK-659), serum lipase and amylase are part of the compulsory safety laboratory tests. Additionally, any other chemistry value that was considered before as abnormal and clinically meaningful can be performed locally for dosing decisions. Unscheduled or repeat laboratory evaluations may be performed locally but also should be collected for central analysis. Clinical laboratory evaluations to be performed are outlined in the tables below.

Handling of clinical laboratory samples will be outlined in the Study Manual.

10.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 10.a, blood samples for analysis of the coagulation parameters shown in Table 10.b, and urine samples for analysis of the parameters shown in Table 10.c will be obtained as specified in the SOEs (Appendix A).

Table 10.a Hematology and Clinical Chemistry Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	γ-glutamyl transferase (GGT)
Leukocytes with differential	ALT	Glucose
Neutrophils (ANC)	Amylase (Screening only, except in Cohort A, which is at each scheduled clinical chemistry)	Lactate dehydrogenase (LDH)
Platelet (count)	AST	Lipase (Screening only, except in Cohort A, which is at each scheduled clinical chemistry)
	Bilirubin (total)	Magnesium
	Blood urea nitrogen (BUN)	Phosphate
	Calcium	Potassium
	Carbon dioxide (CO_2)	Sodium
	Creatinine	Urate

Table 10.b Clinical Coagulation Tests

Coagulation	
Activated partial thromboplastin time (aPTT)	Prothrombin time/international normalized ratio (PT/INR)

Table 10.c Clinical Urinalysis Tests

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

10.4.13.2 Fasting Lipid Profile

Prospective monitoring for hyperlipidemia will be managed through fasting lipid testing at the time points specified in the Schedule of Events (Appendix A).

The fasting lipid profile includes the following:

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

Sampling for the fasting lipid profile will be obtained at the times specified in the Schedule of Events (Appendix A).

10.4.13.3 Fasting Serum Glucose

Fasting serum glucose will be measured at the time points specified in the Schedule of Events (Appendix A) before administration of study drugs.

- Patients are required to fast overnight (nothing except water and/or medications after midnight) or for 8 hours minimum.
- On Cycle 1 Day 1 (Cohorts A and B only) and Cycle 1 Day 2 (Cohorts C and D only), patients will be required to fast for 2 hours after dosing, until the completion of the 2-hour postdose fasting glucose sample. On all other dosing days, the patient is only required to fast for 1 hour postdose.
- Samples for fasting glucose will be obtained at the times specified in the Schedule of Events (Appendix A).

[redacted]

10.4.14 In-Home Daily Fasting Glucose Monitoring

Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 9.8.2 for further instruction.

10.4.15 Pharmacokinetic Measurements

Serial PK samples will be collected at various time points during Part 1 of the study (as specified in Appendix Table A) to characterize the PK of MLN1117, alisertib, and TAK-659 only.

As permitted by the data, PK parameters, including C_{max}; t_{max}; area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_t); area under the plasma concentration-time curve from time 0 to infinity (AUC_∞), calculated as $AUC_\infty = AUC_t + C_{last}/\lambda_z$ (AUC_∞); terminal elimination half-life ($t_{1/2}$); and apparent clearance after extravascular administration, calculated as dose/AUC_∞ after a single dose and as dose/AUC_τ after multiple dosing (at steady state) (CL/F), will be generated using noncompartmental methods.

The primary purpose of PK assessments in this study is to characterize the PK of MLN1117, TAK-659, and alisertib. However, if considered necessary to confirm treatment assignments or to further understand the disposition of the study drugs being evaluated in the patient population enrolled in this study, a subset of the PK samples may be used additionally, pending technical feasibility, to measure concentrations of paclitaxel, docetaxel, and/or metabolites of MLN1117, TAK-659, or alisertib.

Additionally, sparse PK samples will be collected during Part 2 of the study to characterize the PK of MLN1117, alisertib, and TAK-659 (Appendix Table B and Table C). The sparse PK data collected in this study may be pooled with similar data collected in other studies for future population PK analysis (to understand the effect of intrinsic and extrinsic factors on PK and to contribute to analyses of exposure-response relationships for safety and/or efficacy). The results of such population analyses will not be presented in the clinical study report but will be reported separately.

10.4.16 DNA Measurements

Plasma samples will be collected at the time points specified in the SOEs (Appendix A).

[redacted]

In addition, blood samples will be collected for extracting germline DNA to be used as a comparator for mutations detected in tumor samples.

10.4.17 Banked Tumor Specimen Measurements

An archival tumor tissue sample needs to be available for enrollment in Part 2. Archival tumor tissue will be collected from Part 1 patients whenever possible. [redacted]

10.4.18 Tumor Biopsies

For Part 2, access to a tumor tissue sample is required. If a patient does not have archived tumor tissue for evaluation of the EBV status and analysis of biomarkers, a new fresh pretreatment biopsy is required. Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an activated partial thromboplastin time (aPTT) and prothrombin time (PT) within the normal range; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible.

10.4.19 Disease Assessment

Patients will undergo CT scan, with contrast as appropriate, or MRI scan to monitor and assess disease progression, using RECIST, Version 1.1 [3] as outlined in the Schedule of Events (Appendix A).

Determination of disease status will be based on local investigator assessment. The collection and central storage of scans are planned in the event that more detailed analysis of imaging data, as determined by the sponsor, is needed. To support the potential exploratory [redacted] as described in Section 14.1.6.2, prestudy scans, if available, may be collected at the sponsor's discretion.

10.4.20 Pharmacodynamic Measurements

Pharmacodynamic measurements will not be performed in this study.

10.5 Completion of Treatment

Patients will be considered to have completed treatment if they discontinue study drug for any of the reasons outlined in Section 10.7.

[redacted]

10.6 Completion of Study

Patients will be considered to have completed the study if they complete a minimum of 6 cycles of treatment with MLN1117 and any of the combination partners and complete follow-up for PFS or OS as described in Section 10.10. Patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section 10.8.

10.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Study drug may be permanently discontinued for patients meeting any of the following criteria:

- Adverse event.
- Protocol violation.
- Progressive disease.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

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

Patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these will remain in the study for posttreatment assessments as outlined in the Schedule of Events until disease progression occurs.

10.8 Withdrawal of Patients From Study

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

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.
- Death.
- Other.

[redacted]

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

10.9 Study Compliance

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

Patients will receive a sufficient quantity of study drug for each treatment cycle and a diary in which to record their dosing. The study center staff will check the patient's diary versus the patient's supply of remaining study drug at each study visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

10.10 Posttreatment Follow-up Assessments (Progression-Free Survival and Overall Survival)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 weeks from the EOT visit until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the patient discontinued treatment, whichever occurs first.

After the occurrence of PD or the start of subsequent anticancer therapy, patients will continue to have OS follow-up visits. The OS visits should be conducted every 12 weeks after documented PD until death or until 1 year after the last dose of study drug, whichever occurs first.

Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, social security indexes). In addition, information on the start of another anticancer therapy will be collected.

The EOS visit is to be completed at the time the patient withdraws from the study during the follow-up period. See the Schedule of Events (Appendix A) for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drugs and that occur during the posttreatment follow-up period. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of SAEs.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 Pretreatment Event Definition

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

11.1.2 Adverse Event Definition

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.

11.1.3 Serious Adverse Event Definition

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 in Section 11.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home,

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

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03 [1]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a 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.

PD per se is not considered to be an SAE. However, symptoms or diagnoses likely caused by tumor progression that meet seriousness criteria should be reported as SAEs (eg, pulmonary embolism in the context of PD).

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

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 11.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 11.1) must be reported (see Section 11.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

[redacted]

SAE Reporting Contact Information

Cognizant
US and Canada
Toll-Free Fax #: PPD
E-mail: PPD

All Other Countries (Rest of World)
Fax #: PPD
E-mail: PPD

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

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03 [1]. The criteria are provided in the Study Manual.

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

11.3 Monitoring of Adverse Events and Period of Observation

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

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

[redacted]

11.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 11.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 11.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.5 Procedures for Reporting Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses below:

Call center	Phone number	E-mail	Fax	Hours
Dohmen Life Science Services	PPD	PPD	PPD	Mon-Fri 9AM-7PM, ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Cognizant (refer to Section 11.2).

12.0 STUDY-SPECIFIC COMMITTEES

For Part 1, patient information will be discussed in regularly scheduled meetings with investigators, other site personnel, and sponsor representatives. The main outcomes of these meetings are DLT evaluation, dose escalation decisions, patient allocation, and determination of the MTD or recommended dose for Part 2. Meetings will be documented in minutes that require approval by the voting members. For more details, refer to the Cohort Management Plan.

For Part 2 a Steering Committee (SC) will be formed. The sponsor will select up to 5 investigators for periodic review of enrollment and ongoing clinical data with special focus on safety. These meetings will be documented in minutes that require approval by the voting members and will be distributed to all participating investigators. The SC can issue recommendations about the conduct of the study and the need for changes in the protocol and/or ICF.

13.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

13.1 eCRFs

Completed eCRFs are required for each subject who receives study drug.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

13.2 Record Retention

The investigator agrees to keep the records stipulated in Section 13.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site

and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

14.0 STATISTICAL METHODS

14.1 Statistical and Analytical Plans

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

Details for the statistical analysis will be provided in the statistical analysis plan (SAP). The SAP will be written by Takeda and finalized before database lock for the final analysis.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

14.1.1 Analysis Sets

The populations used for analysis will include the following:

- **Safety population**: The Safety population is defined as all patients who receive at least 1 dose of MLN1117+TAK-659 or 1 dose of MLN1117+alisertib or 1 dose of MLN1117+paclitaxel or 1 dose of MLN1117+docetaxel. Patients will be analyzed according to the treatment actually received.
- **Intent-to-Treat (ITT) population**: In Part 2, the ITT population is defined as all patients who are randomized and receive at least 1 dose of any study drug. For the TAK-659 cohort, the ITT population is defined as all patients who receive at least 1 dose of any of the study drugs. The ITT population will be used for the analysis of PFS, TTP, and OS. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.
- **Response-Evaluable population**: The Response-Evaluable population is defined as all patients with gastric cancer, with measurable disease at baseline, who receive at least 1 dose of MLN1117 plus 1 of the combination partners and have at least 1 postbaseline response assessment. The Response-Evaluable population will be used for the analysis of RR (CR+PR), disease control rate (CR+PR+SD), and DOR.
- **DLT-Evaluable population**: The DLT-Evaluable population, defined as all patients in Part 1 (dose escalation) of the study who either experience DLT during Cycle 1 or complete treatment with at least 75% of the planned doses of MLN1117 and the combination partner, and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred, will be used for the analysis of DLT.
- **PK-Evaluable population**: The population of patients evaluable for the determination of the PK of MLN1117 is defined as all patients in Part 1 (dose escalation of the study for whom there are sufficient dosing and MLN1117 concentration-time data to permit noncompartmental PK analysis.

[redacted]

14.1.2 Randomization and Stratification

In the dose escalation phase (Part 1), there is no randomization; all patients will receive MLN1117+TAK-659 (Cohort A) or MLN1117+alisertib (Cohort B) or MLN1117+paclitaxel (Cohort C) or MLN1117+docetaxel (Cohort D). Details regarding patient allocation are provided in the Cohort Management Plan document.

In the dose expansion phase (Part 2), patients who are EBV positive will be assigned to treatment with TAK-659 in combination with MLN1117 (Cohort A). For patients who are EBV negative, there will be 2 parts to the randomization phase. Patients initially will be randomized equally to 1 of the other treatment cohorts, 5 patients per group: MLN1117+alisertib (Cohort B), MLN1117+paclitaxel (Cohort C), or MLN1117+docetaxel (Cohort D). These patients will be assessed using a proportional weighted clinical utility function (allocating specific weights for CR, PR, SD, and PD. Initially, the clinical utility function will assign weights for CR=5, PR=2, SD=1, and PD=0; after 6 months of having CR, PR, and SD, weights will increase to CR=6, PR=4, SD=2, and PD weighting will remain the same. Patients then will be randomized to treatment according to an adaptive randomization algorithm, which incorporates weighted clinical utility function. The resulting probability will continually be updated per accumulating data. Adaptive randomization will be applied to newly enrolling patients every 2 months based on cumulative data.

The randomization scheme will be generated by an independent statistician at Takeda who is not on the study team. Before dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an IWRS. The proportional weighted utility function based on response assessment will be calculated by the study statistician at Takeda and the assignment of treatment group ratios will be implemented through IWRS.

Stratification will not be used in this study.

14.1.3 Analysis of Demographics and Other Baseline Characteristics

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, gender, race, weight, baseline disease characteristics, histology, and genotype status.

14.1.4 Efficacy Analysis

14.1.4.1 Analysis of Primary Efficacy Endpoints

Dose Escalation Phase (Part 1)

There is no primary efficacy endpoint in the dose escalation portion of the study.

Dose Expansion Phase (Part 2)

The primary efficacy endpoint for the dose expansion portion is ORR, defined as CR+PR. The estimate of the RR will be presented with 2-sided 95% exact binomial CIs for each treatment arm. The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, Version 1.1 [3]. Fisher's exact tests will be performed for the

comparison of RR between the treatment arms. RR will be analyzed based on the Response-Evaluable population.

14.1.4.2 Analysis of Secondary Efficacy Endpoints

Dose Escalation Phase (Part 1)

The secondary efficacy endpoint in the dose escalation portion of the study is the ORR, defined as CR+PR, which will be presented in a listing.

Dose Expansion Phase (Part 2)

The secondary endpoints in the phase 2 portion of the study include PFS, disease control rate (CR+PR+SD), DOR, TTP, and OS. PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. The censoring method will be described in the SAP. PFS will be tested based on the ITT population. An unstratified log-rank test will be used to compare the treatment arms with respect to PFS. In addition, a Cox regression model will be used to estimate the hazard ratio and its 95% CI for the treatment effect. The Kaplan-Meier survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment arm.

Disease control rate is defined as CR+PR+SD. The estimate of the disease control rate will be presented with 2-sided 95% exact binomial CIs for each treatment arm. The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, Version 1.1 [3]. Fisher's exact tests will be performed for the comparison of disease control rate between the treatment arms. Disease control rate will be analyzed based on the Response-Evaluable population.

DOR is defined as the time from the date of first documentation of a response to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

TTP is defined as the time from the date of randomization to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

OS is defined as the time from the date of randomization to the date of death from any cause.

DOR, TTP, and OS will be analyzed using the Kaplan-Meier method. Unstratified long-rank tests will be performed for the comparisons between the 2 treatment arms. DOR will be analyzed based on the responders in the Response-Evaluable population. TTP and OS will be analyzed using the ITT population.

14.1.5 Pharmacokinetic Analysis

Individual and mean plasma concentration data collected during Part 1 (dose escalation) will be plotted over time as follows:

MLN1117+TAK-659

Individual and mean MLN1117 and TAK-659 plasma concentration data collected during Part 1 (dose escalation) will be plotted over time for Cycle 1 Day 1 and Cycle 1 Day 17.

Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters, including C_{max}, AUC_{last}, AUC_{inf}, and $t_{½}$ for MLN1117 and TAK-659 as permitted by the data. Descriptive statistics will be presented for plasma PK parameters of MLN1117 and TAK-659 by day and by time.

MLN1117+alisertib

Individual and mean MLN1117 and alisertib plasma concentration data collected during Part 1 (dose escalation) will be plotted over time for Cycle 1 Day 3.

Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters, including C_{max}, AUC_{last}, AUC_{inf}, and $t_{½}$ for MLN1117 and alisertib as permitted by the data. Descriptive statistics will be presented for plasma PK parameters of MLN1117 and alisertib by day and by time.

MLN1117+docetaxel and MLN1117+paclitaxel

Individual and mean MLN1117 plasma concentration data collected during Part 1 (dose escalation) will be plotted over time for Cycle 1 Day 2.

Noncompartmental PK analysis will be performed on individual concentration-time data to calculate plasma PK parameters, including C_{max}, AUC_{last}, AUC_{inf}, and $t_{½}$ for MLN1117 as permitted by the data. Descriptive statistics will be presented for plasma PK parameters of MLN1117 by day and by time. The serial PK of paclitaxel or docetaxel is not being collected in this study and will not be reported.

Sparse PK data during Part 2 (dose expansion) of the study will be collected for all patients at the prespecified time points outlined in Appendix Table B and Table C. Plasma concentration data for individual patients will be provided in listings. The sparse PK data collected during Part 2 of the study may be combined with similar data in other studies for the purposes of future population PK analysis.

14.1.6 Exploratory Analysis

14.1.6.1 Exploratory Endpoints

[redacted]

14.1.6.2 [redacted]

[redacted]

[redacted]

14.1.7 Biomarker Analysis

Descriptive statistics, graphical methods, and statistical modeling as appropriate will be used to explore the relationship between response and the levels of various biomarkers.

14.1.8 Safety Analysis

The incidence of DLT will be tabulated for each dose group. In addition, to assess the relationship between toxicities and MLN1117 dose, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group. The DLT-evaluable population will be used for the analysis of DLT.

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

TEAEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

AEs will be tabulated according to the MedDRA and will include the following categories:

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

[redacted]

- Drug-related SAEs.

A listing of TEAEs resulting in study drug discontinuation will be provided.

Descriptive statistics for actual values of clinical laboratory parameters (and/or change from baseline) will be presented for all scheduled measurements over time. Central laboratory test values will be used for the safety analysis. Mean laboratory values over time will be plotted for key laboratory parameters. Creatinine clearance, will be derived by the sponsor using Cockcroft-Gault equation (see Appendix D), will also be assessed as a laboratory parameter.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point. Shift tables for laboratory parameters will be generated on the basis of changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values and/or e-dish plots, may be used to understand the safety profile of the combinations.

All concomitant medications collected from the first dose throughout the study period will be summarized by preferred term according to the WHO drug dictionary.

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point including any unscheduled measurements.

ECOG performance status and change from baseline will be summarized. Shifts from baseline to the worst postbaseline score will be tabulated by treatment arm.

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

14.1.9 Procedures for Handling Missing, Unused, and Spurious Data

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

14.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned for this study.

14.3 Determination of Sample Size

14.3.1 Dose Escalation Phase (Part 1)

The number of patients enrolled in this study will be driven initially by the dose escalation part and by the dose expansion part. In Part 1 (dose escalation), approximately 15 patients may be enrolled in each combination treatment group, with potentially 3 to 6 patients in each dose cohort. Therefore, approximately 60 patients may be enrolled in the dose escalation phase.

[redacted]

14.3.2 Dose Expansion Phase (Part 2)

All patients who enter Part 2 of the study will be screened to determine whether or not their tumor tissue is positive for EBV (approximately 9% of patients with gastric cancer). An estimated 28 patients who are EBV positive will be assigned to treatment with TAK-659 in combination with MLN1117 (Cohort A). The sample size is estimated based on the following parameters: a 1-sided test at the significance level of alpha=0.05, power of 75%, a null hypothesis of RR=10%, and an alternative hypothesis of RR=25%. Based on a single proportion test, 28 evaluable patients need to be enrolled in Cohort A. For patients who are EBV negative, there will be 2 parts to the randomization phase. Patients initially will be randomized equally to 1 of the other treatment cohorts, 5 patients per group: MLN1117+alisertib (Cohort B), MLN1117+paclitaxel (Cohort C), or MLN1117+docetaxel (Cohort D). These patients will be assessed using a proportional weighted clinical utility function (allocating specific weights for CR, PR, SD, and PD. Initially the clinical utility function will assign weights for CR=5, PR=2, SD=1 and PD=0; after 6 months of having CR, PR, or SD, weights will increase to CR=6, PR=4, SD=2, and PD weighting will remain the same. Patients then will be randomized to treatment according to an adaptive randomization algorithm, which incorporates weighted clinical utility function. The resulting probability will continually be updated per accumulating data on the associations between the ORR and Bayesian stopping rules (defined below). Adaptive randomization will be applied to newly enrolling patients every 2 months based on cumulative data. The adaptive randomization will increase the opportunity for each patient to receive the most effective experimental treatment possible based on posterior probabilities. Simulations results for adaptive randomization using clinical utility function and Bayesian stopping rules will be described in the SAP. Up to an additional 25 patients may be enrolled in each treatment regimen. Based on simulation results, the sample size for Part 2 (the umbrella portion) may be between 61 and 90 patients. Therefore, a maximum number of 118 patients may be enrolled in the dose expansion phase.

ORR will be used as the efficacy benchmark: target 25% (0.25); undesirable 10% (0.1). Early stopping rules will be prespecified if there is a clear signal of efficacy or lack of efficacy. The stopping rules are as follows:

1. Achieve maximum sample size of each arm (30 patients).
2. Select an arm if probability (Pr), Pr (RR>0.25/Data) >80% and Pr (RR>0.10)/Data) >90%.
3. Suspend accrual to an arm if Pr (RR≤0.10/Data) >80%.

The treatment arm(s) is/are chosen in relation to the efficacy bar prespecified (target and undesirable); therefore, it is possible to select multiple treatment arms per this study design.

[redacted]

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

15.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

15.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 15.1.

[redacted]

16.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

16.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

[redacted]

16.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

[redacted]

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

16.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 16.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

16.4 Publication, Disclosure, and Clinical Trial Registration Policy

16.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

[redacted]

16.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

16.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

16.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

17.0 REFERENCES

1. Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services Series v4.03. June 14, 2010. Publication No. 09-5410.
2. The Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513:202-9.
3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
4. Yao Z, Guo H, Yuan Y, Zhao Y, Yao S, Xu Y, et al. Retrospective analysis of docetaxel, oxaliplatin plus fluorouracil compared with epirubicin, cisplatin and fluorouracil as first-line therapy for advanced gastric cancer. J Chemother 2014;26(2):117-21.
5. Chen XL, Chen XZ, Yang C, Liao YB, Li H, Wang L, et al. Docetaxel, cisplatin and fluorouracil (DCF) regimen compared with non-taxane-containing palliative chemotherapy for gastric carcinoma: a systematic review and meta-analysis. PLoS One 2013;8(4):e60320.
6. Inal A, Kaplan MA, Kucukoner M, Isikdogan A. Docetaxel and Cisplatin Plus Fluorouracil compared with Modified Docetaxel, Cisplatin, and 5-Fluorouracil as first-line therapy for advanced gastric cancer: a retrospective analysis of single institution. Neoplasma 2012;59(2):233-6.
7. Pasini F, Fraccon AP, G DEM. The role of chemotherapy in metastatic gastric cancer. Anticancer Res 2011;31(10):3543-54.
8. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24(31):4991-7.
9. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358(1):36-46.
10. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14(6):481-9.
11. Sendur MA, Ozdemir N, Ozatli T, Yazici O, Aksoy S, Ekinci AS, et al. Comparison the efficacy of second-line modified EOX (epirubicin, oxaliplatin, and capecitabine) and irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) regimens in metastatic gastric cancer patients that progressed on first-line modified docetaxel and cisplatin plus fluorouracil (DCF) regimen. Med Oncol 2014;31(9):153.

[redacted]

12. Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9(1):14-8.
13. Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, et al. A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). Anticancer Res 2007;27(4C):2667-71.
14. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 2013;31(35):4438-44.
15. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet 2014;383(9911):31-9.
16. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15(11):1224-35.
17. Zhang C, Awasthi N, Schwarz MA, Schwarz RE. The dual PI3K/mTOR inhibitor NVP-BEZ235 enhances nab-paclitaxel antitumor response in experimental gastric cancer. Int J Oncol 2013;43(5):1627-35.
18. Wallin JJ, Guan J, Prior WW, Lee LB, Berry L, Belmont LD, et al. GDC-0941, a novel class I selective PI3K inhibitor, enhances the efficacy of docetaxel in human breast cancer models by increasing cell death in vitro and in vivo. Clin Cancer Res 2012;18(14):3901-11.
19. Burris HA, 3rd. Overcoming acquired resistance to anticancer therapy: focus on the PI3K/AKT/mTOR pathway. Cancer Chemother Pharmacol 2013;71(4):829-42.
20. Chen L, Han L, Shi Z, Zhang K, Liu Y, Zheng Y, et al. LY294002 enhances cytotoxicity of temozolomide in glioma by down-regulation of the PI3K/Akt pathway. Molecular Medicine Reports 2012;5(2):575-9.
21. VanderWeele DJ, Zhou R, Rudin CM. Akt up-regulation increases resistance to microtubule-directed chemotherapeutic agents through mammalian target of rapamycin. Mol Cancer Ther 2004;3(12):1605-13.
22. Pandey A, Kulkarni A, Roy B, Goldman A, Sarangi S, Sengupta P, et al. Sequential application of a cytotoxic nanoparticle and a PI3K inhibitor enhances antitumor efficacy. Cancer Res 2014;74(3):675-85.
23. Hirai H, Sootome H, Nakatsuru Y, Miyama K, Taguchi S, Tsujioka K, et al. MK-2206, an allosteric Akt inhibitor, enhances antitumor efficacy by standard chemotherapeutic agents or molecular targeted drugs in vitro and in vivo. Mol Cancer Ther 2010;9(7):1956-67.

[redacted]

24. Dawson CW, Port RJ, Young LS. The role of the EBV-encoded latent membrane proteins LMP1 and LMP2 in the pathogenesis of nasopharyngeal carcinoma (NPC). Semin Cancer Biol 2012;22(2):144-53.

25. Sobin LH, Gospodarowicz MK, Wittekind C, editors. International Union Against Cancer (UICC) TNM Classification of Malignant Tumours. 7th ed. United Kingdom: Wiley-Blackwell; 2009.

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

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Appendix A Schedules of Events

Schedule of Events for MLN1117+TAK-659 (Cohort A) Treatment Arm (28-Day Cycle)

		Cycle 1 (Part 1, Escalation Only)				Cycle 1 (Part 2, Expansion Only)			Cycles 2-4		Cycles 5 and Beyond		
			Day				Day		Day				
	Screening (a)	Day 1 Predose	2 (PK only)	8	17	Day 1 Predose	8	15	1	15	Day 1	EOT	PFSFU/ OSFU
Informed consent (b)	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history	X												
Physical examination (c)	X	X		X	X	X	X	X	X	X	X	X	
Height	X												
Weight	X	X				X			X		X	X	
Vital signs (d)	X	X		X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X				X			X		X	X	
12-lead ECG (e)	X	X				X			X		X	X	
Monitoring of concomitant medications and procedures (f)		Recorded from first dose of study drug through 30 days after the last dose of study drug.											
Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug.											
Serious adverse event reporting (g)	**Serious adverse events** will be reported from signing of the informed consent form through 30 days after the last dose of study drug.												
Study drug administration		TAK-659 (Dose TBD) PO continuous daily dosing in combination with MLN1117 (starting dose of 300 mg) PO 3 days on (Days 1-3) and 4 days off per week in a 28-day cycle.											
Patient diary review (h)		X		X	X	X	X	X	X	X	X	X	
Samples/Laboratory Assessments													
Pregnancy test (i)	X	X				X							
Hematology (j)	X	X		X	X	X	X	X	X	X	X	X	
Chemistry (j)	X	X		X	X	X	X	X	X	X	X	X	
Coagulation (j)	X	X				X			X		X		
Urinalysis	X	X				X			X		X	X	

[redacted]

Schedule of Events for MLN1117+TAK-659 (Cohort A) Treatment Arm (28-Day Cycle)

		Cycle 1 (Part 1, Escalation Only)				Cycle 1 (Part 2, Expansion Only)			Cycles 2-4		Cycles 5 and Beyond		
			Day				Day		Day				
	Screening (a)	Day 1 Predose	2 (PK only)	8	17	Day 1 Predose	8	15	1	15	Day 1	EOT	PFSFU/ OSFU
Fasting serum glucose (j,k)	X	X		X	X	X	X	X	X	X (l)	X	X	
Fasting lipid profile	X								Day 1 of Cycle 3 and every 3 cycles thereafter.				
HbA1c	X								Day 1 of Cycle 3 and every 3 cycles thereafter.				
In-home daily fasting glucose monitoring (m)		See footnote m.											
Blood sample for PK (n, o)		X (n)	X (n)		X (n)					X (o)			
Plasma ctDNA (p)	X								Plasma will be collected on Day 1 of Cycle 3 and every 2 cycles thereafter.				
Blood sample germline DNA (t)	X												
Banked tumor tissue or fresh biopsy sample (q)	X												
Disease Assessment													
Disease evaluation by RECIST, Version 1.1 (CT/MRI) (r)	X								Disease assessment to be conducted during Days 25-28 at the end of Cycles 2, 4, 6, and every other cycle thereafter.				X q 12 wk
OS follow-up (OS and subsequent anticancer therapy) (s)													X q 12 wk

CxDx=Cycle x Day x, CT=computed tomography, ctDNA=circulating tumor deoxyribonucleic acid, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End of Treatment, HbA1c=glycosylated hemoglobin, MRI=magnetic resonance imaging, OS=overall survival, OSFU=overall survival follow-up, PD=progressive disease, PFS=progression-free survival, PFSFU=progression-free survival follow-up, PK=pharmacokinetic(s), PO=orally, RECIST=Response Evaluation Criteria in Solid Tumors.

(a) The Screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

(b) The informed consent form (ICF) may be signed more than 28 days prior to C1D1, but has to be signed before any study-required procedures are conducted, unless those

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procedures are performed as part of the patient's standard care
(c) A complete physical examination should be performed at screening and EOT. A symptom-directed physical examination should be performed on all other days as specified above.
(d) Vital signs measurements should be obtained at screening and on all other days as specified above. Vital signs include blood pressure, heart rate, and temperature.
(e) Single 12-lead ECGs will be obtained. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, then the ECG will be completed before the collection of the blood sample.
(f) See Section 9.5 for medications and procedures that are prohibited during the study, and Section 9.6 for medications that should be used cautiously during the study.
(g) Only those serious adverse events (SAEs) that occur after the first dose of study drug will be collected in the electronic case report form; however, all SAEs occurring after consent will be reported. See Section 10.4.11.
(h) The study center staff will check the patient diary versus the patient's supply of MLN1117 and TAK-659 tablets to assess compliance.
(i) A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on C1D1 with negative results available before the first dose of the study drug may be administered. A serum pregnancy test may also be performed within 3 days of dosing in place of the C1D1 urine test.
(j) Samples may be collected up to 3 days before the scheduled visit except for Cycle 1 Day 1. See Section 10.4.13.1 for the full hematology, coagulation, and clinical chemistry panels.
(k) Fasting serum glucose collected prior to MLN1117 dosing in every cycle, and at 2 hours post dosing only on Cycle 1 Day 1.
(l) The only exception to (k) is in Part 2, Cycle 2 Day 15, when patients will take the study drugs at home before coming to the clinic for sparse PK sample collection.
(m) Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 9.8.2 for further instruction.
(n) Patients in Part 1 (dose escalation) of the study will return to the clinic to have their PK samples collected as specified in Appendix Table A.
(o) Patients in Part 2 (dose expansion) of the study will return to the clinic to have their sparse PK samples collected as specified in Appendix Table B.
(p) A blood sample for plasma will be obtained at screening and as specified above for evaluation of circulating tumor DNA.
(q) Collection of tumor tissue (banked) will be requested (Part 1) and required (Part 2) at screening as specified in Section 10.4.17. For banked tissue, the sample can be from either paraffin-embedded tumor block or unstained slides. If a paraffin-embedded tumor block or unstained slides are not available, the patient will be required to undergo a fresh tumor biopsy as specified in Section 10.4.18 (Part 2 only). The sample must be collected during screening before the first dose of study drug. Epstein-Barr virus (EBV) testing must be performed on all Part 2 (dose expansion) patients prior to randomization. In addition, tumor tissue will be analyzed and will be tested retrospectively for genetic mutations and amplifications.
(r) Response assessments will be performed on Days 25-28 at the end of treatment of Cycles 2, 4, 6, and then every 2 cycles thereafter until the patient discontinues study drug due to disease progression, unacceptable toxicity, or death. A CT scan with intravenous contrast of the chest, abdomen, and pelvis will be performed during screening (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study). If the patient has had an appropriate CT or MRI scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening. Patients who discontinue study drug treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study drug treatment, whichever occurs first.
(s) OS is to be assessed every 12 weeks until patient death or 1 year after the patient's last dose of study drug, whichever occurs first.
(t) Blood samples will be collected at screening for extracting germline DNA to be used as a comparator for mutations in tumor samples.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) with permission of the project clinician for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician.**

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Schedule of Events for MLN1117+Alisertib (Cohort B) Treatment Arm (28-Day Cycle)

		Cycle 1 (Part 1, Escalation Only)						Cycle 1 (Part 2, Expansion Only)			Cycles 2 and Beyond			
			Day					Day			Day			
	Screening (a)	Day 1 Predose	3 (PK only)	4 (PK only)	8	15	22	1	8	15	1	15	EOT	PFSFU/ OSFU
Informed consent (b)	X													
Inclusion/exclusion criteria	X													
Demographics	X													
Medical history	X													
Physical examination (c)	X	X			X	X	X	X	X	X	X	X	X	
Height	X													
Weight	X	X						X			X		X	
Vital signs (d)	X	X			X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X						X			X		X	
12-lead ECG (e)	X	X						X			X		X	
Monitoring of concomitant medications and procedures (f)			Recorded from first dose of study drug through 30 days after the last dose of study drug.											
Adverse event reporting			Recorded from first dose of study drug through 30 days after the last dose of study drug.											
Serious adverse event reporting (g)	**Serious adverse events** will be reported from signing of the informed consent form through 30 days after the last dose of study drug.													
Study drug administration		Alisertib (40 mg PO BID) 3 days on (Days 1-3) and 4 days off per week (during Weeks 1, 2, and 3), 1 week off in a 28-day cycle in combination with MLN1117 (starting dose 300 mg) PO 3 days on (Days 1-3) and 4 days off per week in a 28-day cycle.												
Patient diary review (h)		X			X	X	X	X	X	X	X	X	X	
Samples/Laboratory Assessments														
Pregnancy test (i)	X	X						X						
Hematology (j)	X	X			X	X	X	X	X	X	X	X	X	
Chemistry (j)	X	X			X	X	X	X	X	X	X	X	X	
Coagulation (j)	X	X						X			X			
Urinalysis	X	X						X			X		X	

[redacted]

Schedule of Events for MLN1117+Alisertib (Cohort B) Treatment Arm (28-Day Cycle)

		Cycle 1 (Part 1, Escalation Only)						Cycle 1 (Part 2, Expansion Only)			Cycles 2 and Beyond			
			Day					Day			Day			
	Screening (a)	Day 1 Predose	3 (PK only)	4 (PK only)	8	15	22	1	8	15	1	15	EOT	PFSFU/ OSFU
Fasting serum glucose (j, k)	X	X			X	X	X	X	X	X	X	X (l)	X	
Fasting lipid profile	X										Day 1 of Cycle 3 and every 3 cycles thereafter.			
HbA1c	X										Day 1 of Cycle 3 and every 3 cycles thereafter.			
In-home daily fasting glucose monitoring (m)		See footnote m.												
Blood samples for PK (n, o)			X (n)	X (n)								X (o)		
Plasma ctDNA (p)	X										Plasma will be collected on Day 1 of Cycle 3 and every 2 cycles thereafter.			
Blood sample germline DNA (t)	X													
Banked tumor tissue or fresh biopsy sample (q)	X													
Disease Assessment														
Disease evaluation by RECIST, Version 1.1 (CT/MRI) (r)	X										Disease assessment to be conducted during Days 25-28 at the end of Cycles 2, 4, 6 and every other cycle thereafter.			X q 12 wk
OS follow-up (OS and subsequent anticancer therapy) (s)														X q 12 wk

[redacted]

BID=twice daily, CxDx=Cycle x Day x, CT=computed tomography, ctDNA=circulating tumor deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End of Treatment, HbA1c=glycosylated hemoglobin, MRI=magnetic resonance imaging, OS=overall survival, OSFU=overall survival follow-up, PD=progressive disease, PFS=progression-free survival, PFSFU=progression-free survival follow-up, PK=pharmacokinetic(s), PO=orally, RECIST=Response Evaluation Criteria in Solid Tumors.

(a) The Screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

(b) The informed consent form (ICF) may be signed more than 28 days prior to C1D1, but has to be signed before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

(c) A complete physical examination should be performed at screening and EOT. A symptom-directed physical examination should be performed on all other days as specified above.

(d) Vital signs measurements should be obtained at screening and on all other days as specified above. Vital signs include blood pressure, heart rate, and temperature.

(e) Single 12-lead ECGs will be obtained. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, then the ECG will be completed before the collection of the blood sample.

(f) See Section 9.5 for medications and procedures that are prohibited during the study and Section 9.6 for medications that should be used cautiously during the study.

(g) Only those serious adverse events (SAEs) that occur after the first dose of study drug will be collected in the electronic case report form; however, all SAEs occurring after consent will be reported. See Section 10.4.11.

(h) The study center staff will check the patient diary versus the patient's supply of MLN1117 tablets and alisertib tablets to assess compliance.

(i) A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on C1D1 with negative results available before the first dose of the study drug may be administered. A serum pregnancy test may also be performed within 3 days of dosing in place of the C1D1 urine test.

(j) Samples may be collected up to 3 days before the scheduled visit except for Cycle 1 Day 1. See Section 10.4.13.1 for the full hematology, coagulation, and clinical chemistry panels.

(k) Fasting serum glucose collected prior to MLN1117 dosing in every cycle, and at 2 hours post dosing only on Cycle 1 Day 1.

(l) The only exception to (k) is Part 2, Cycle 2 Day 15, when patients will take the study drugs at home before coming to the clinic for sparse PK sample collection.

(m) Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 9.8.2 for further instruction.

(n) Patients in Part 1 (dose escalation) of the study will return to the clinic to have their PK samples collected as specified in Table A.

(o) Patients in Part 2 (dose expansion) of the study will return to the clinic to have their sparse PK samples collected as specified in Table B.

(p) A blood sample for plasma will be obtained at screening and as specified above for evaluation of circulating tumor DNA.

(q) Collection of tumor tissue (banked) will be requested (Part 1) and required (Part 2) at screening as specified in Section 10.4.17. For banked tissue, the sample can be from either paraffin-embedded tumor block or unstained slides. If a paraffin-embedded tumor block or unstained slides are not available, the patient will be required to undergo a fresh tumor biopsy as specified in Section 10.4.18 (Part 2 only). The sample must be collected during screening before the first dose of study drug. Epstein-Barr virus (EBV) testing must be performed on all Part 2 (dose expansion) patients prior to randomization. In addition, tumor tissue will be analyzed and will be tested retrospectively for genetic mutations and amplifications.

(r) Response assessments will be performed on Days 25-28 at the end of treatment of Cycles 2, 4, 6, and then every 2 cycles thereafter until the patient discontinues study drug due to disease progression, unacceptable toxicity, or death. A CT scan with intravenous contrast of the chest, abdomen, and pelvis will be performed during screening (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study). If the patient has had an appropriate CT or MRI scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening. Patients who discontinue study drug treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study drug treatment, whichever occurs first.

[redacted]

(s) OS is to be assessed every 12 weeks until patient death or until 1 year after the last dose of study drug, whichever occurs first.
(t) Blood samples will be collected at screening for extracting germline DNA to be used as a comparator for mutations in tumor samples.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) with permission of the project clinician for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician.**

[redacted]

Schedule of Events for MLN1117+Paclitaxel (Cohort C) Treatment Arm (28-Day Cycle)

		Cycle 1 (Part 1+Part 2)						Cycles 2-6			Cycles 7 and Beyond		
			Day					Day					
	Screening (a)	Day 1 Predose	2	3 (Part 1 PK only)	8	9 (Part 2 PK only)	15	1	8	15	Day 2 (first dose of MLN1117)	EOT	PFSFU/ OSFU
Informed consent (b)	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history	X												
Physical examination (c)	X	X	X		X		X	X	X	X	X	X	
Height	X												
Weight	X	X						X			X	X	
Vital signs (d)	X	X	X		X		X	X	X	X	X	X	
ECOG performance status	X	X						X			X	X	
12-lead ECG (e)	X	X						X			X	X	
Monitoring of concomitant medications and procedures (f)		Recorded from first dose of study drug through 30 days after the last dose of study drug.											
Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug.											
Serious adverse event reporting (g)	**Serious adverse events** will be reported from signing of the informed consent form through 30 days after the last dose of study drug.												
Study drug administration (r)		Paclitaxel (80 mg/m^2) IV once weekly on Days 1, 8, and 15, and 1 week off, in a 28-day cycle, in combination with MLN1117 (starting dose 300 mg) PO 3 days on (Days 2-4, 9-11, 16-18, 23-25) and 4 days off per week, in a 28-day cycle. **At Cycle 7 and beyond, only MLN1117 will be administered (see footnote r).**											
Patient diary review (h)		X			X		X	X	X	X	X	X	
Samples/Laboratory Assessments													
Pregnancy test (i)	X	X											
Hematology (j)	X	X	X		X		X	X	X	X	X	X	
Chemistry (j)	X	X	X		X		X	X	X	X	X	X	

[redacted]

Schedule of Events for MLN1117+Paclitaxel (Cohort C) Treatment Arm (28-Day Cycle)

		Cycle 1 (Part 1+Part 2)						Cycles 2-6			Cycles 7 and Beyond		
			Day					Day					
	Screening (a)	Day 1 Predose	2	3 (Part 1 PK only)	8	9 (Part 2 PK only)	15	1	8	15	Day 2 (first dose of MLN1117)	EOT	PFSFU/ OSFU
Coagulation (j)	X	X						X			X		
Urinalysis	X	X						X			X	X	
Fasting serum glucose (j, k)	X	X	X		X		X	X	X	X	X	X	
Fasting lipid profile	X							Day 1 of Cycles 3 and 6; Day 2 of Cycle 9 and every 3 cycles thereafter.					
HbA1c	X							Day 1 of Cycles 3 and 6; Day 2 of Cycle 9 and every 3 cycles thereafter.					
In-home daily fasting glucose monitoring (l)		See footnote l.											
Blood samples for PK (m)			X	X		X							
Plasma ctDNA (n)	X							Plasma will be collected on Day 1 of Cycles 3 and 5, and on Day 2 of Cycle 7 and every 2 cycles thereafter.					
Blood sample germline DNA (s)	X												
Banked tumor tissue or fresh biopsy sample (o)	X												
Disease Assessment													
Disease evaluation by RECIST, Version 1.1 (CT/MRI) (p)	X							Disease assessment to be conducted during Days 25-28 at the end of Cycles 2, 4, 6, and every other cycle thereafter.					X q 12 wk
OS follow-up (OS and subsequent anticancer therapy) (q)													X q 12 wk

CxDx=Cycle x Day x, CT=computed tomography, ctDNA=circulating tumor deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End of Treatment, HbA1c=glycosylated hemoglobin, IV=intravenous, MRI=magnetic resonance imaging, OS=overall survival, OSFU=overall survival follow-up, PD=progressive disease, PFS=progression-free survival, PFSFU=progression-free survival follow-up, PK=pharmacokinetic(s), PO=orally, RECIST=Response Evaluation Criteria in Solid Tumors.

(a) The Screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Screening assessments performed no more than 3 days before Day 1 will

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qualify as baseline assessments and need not be repeated, unless otherwise specified.
(b) The informed consent form (ICF) may be signed more than 28 days prior to C1D1, but has to be signed before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.
(c) A complete physical examination should be performed at screening and EOT. A symptom-directed physical examination should be performed on all other days as specified above.
(d) Vital signs should be obtained at screening and on all other days as specified above. Vital signs include blood pressure, heart rate, and temperature.
(e) Single 12-lead ECGs will be obtained. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, then the ECG will be completed before the collection of the blood sample.
(f) See Section 9.5for medications and procedures that are prohibited during the study, and Section 9.6 for medications that should be used cautiously during the study.
(g) Only those serious adverse events (SAEs) that occur after the first dose of study drug will be collected in the electronic case report form; however, all SAEs occurring after consent will be reported. See Section 10.4.11.
(h) The study center staff will check the patient diary versus the patient's supply of MLN1117 tablets to assess compliance.
(i) A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on C1D1 with negative results available before the first dose of the study drug may be administered. A serum pregnancy test may also be performed within 3 days of dosing in place of the C1D1 urine test.
(j) Samples may be collected up to 3 days before the scheduled visit except for Cycle 1 Day 2. See Section 10.4.13.1 for the full hematology, coagulation, and clinical chemistry panels.
(k) Fasting serum glucose collected prior to MLN1117 dosing in every cycle, and at 2 hours post dosing only on Cycle 1 Day 2.
(l) Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 9.8.2 for further instruction.
(m) Patients in Part 1 (dose escalation) of the study will return to the clinic to have their 24-hour PK samples collected as specified in Appendix Table A.
Patients in Part 2 (dose expansion) of the study will return to the clinic to have their sparse PK samples collected as specified in Appendix Table C.
(n) A blood sample for plasma will be obtained at screening and every 2 cycles thereafter for evaluation of circulating tumor DNA.
(o) Collection of tumor tissue (banked) will be requested (Part 1) and required (Part 2) at screening as specified in Section 10.4.17. For banked tissue, the sample can be from either paraffin-embedded tumor block or unstained slides. If a paraffin-embedded tumor block or unstained slides are not available, the patient will be required to undergo a fresh tumor biopsy as specified in Section 10.4.18 (Part 2 only). The sample must be collected during screening before the first dose of study drug. Epstein-Barr virus (EBV) testing must be performed on all Part 2 (dose expansion) patients prior to randomization. In addition, tumor tissue will be analyzed and will be tested retrospectively for genetic mutations and amplifications.
(p) Response assessments will be performed on Days 25-28 at the end of treatment of Cycles 2, 4, 6, and then every 2 cycles thereafter until the patient discontinues study drug due to disease progression, unacceptable toxicity, or death. A CT scan with IV contrast of the chest, abdomen, and pelvis will be performed during screening (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study). If the patient has had an appropriate CT or MRI scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening. Patients who discontinue study drug treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study treatment, whichever occurs first.
(q) OS is to be assessed every 12 weeks until patient death or until 1 year after the last dose of study drug, whichever occurs first.
(r) Paclitaxel may be administered after Cycle 6 if the investigator and sponsor determine that the patient would derive benefit from continued treatment.
(s) Blood samples will be collected at screening for extracting germline DNA to be used as a comparator for mutations in tumor samples.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) with permission of the project clinician for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician.**

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Schedule of Events for MLN1117+Docetaxel (Cohort D) Treatment Arm (21-Day Cycle)

		Cycle 1 (Part 1+Part 2)					Cycles 2-4		Cycles 5-6	Cycles 7 and Beyond		
			Day				Day					
	Screening (a)	Day 1 Predose	2	3 (Part 1 PK only)	9	16	1	9	Day 1	Day 2 (first dose of MLN1117)	EOT	PFSFU/ OSFU
Informed consent (b)	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Medical history	X											
Physical examination (c)	X	X	X		X	X	X	X	X	X	X	
Height	X											
Weight	X	X					X		X	X	X	
Vital signs (d)	X	X	X		X	X	X	X	X	X	X	
ECOG performance status	X	X					X		X	X	X	
12-lead ECG (e)	X	X					X		X	X	X	
Monitoring of concomitant medications and procedures (f)		Recorded from first dose of study drug through 30 days after the last dose of study drug.										
Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug.										
Serious adverse event reporting (g)	**Serious adverse events** will be reported from signing of the informed consent form through 30 days after the last dose of study drug.											
Study drug administration (r)		Docetaxel (75 mg/m^2) IV once every 3 weeks, in a 21-day cycle, in combination with MLN1117 PO 3 days on (Days 2-4, 9-11, 16-18) and 4 days off, in a 21-day cycle. **At Cycle 7 and beyond, only MLN1117 will be administered (see footnote r).**										
Patient diary review (h)		X	X		X	X	X	X	X	X	X	
Samples/Laboratory Assessments												
Pregnancy test (i)	X	X										
Hematology (j)	X	X	X		X	X	X	X	X	X	X	
Chemistry (j)	X	X	X		X	X	X	X	X	X	X	
Coagulation (j)	X	X					X		X	X		
Urinalysis	X	X					X		X	X	X	

[redacted]

Schedule of Events for MLN1117+Docetaxel (Cohort D) Treatment Arm (21-Day Cycle)

		Cycle 1 (Part 1+Part 2)					Cycles 2-4		Cycles 5-6	Cycles 7 and Beyond		
			Day				Day					
	Screening (a)	Day 1 Predose	2	3 (Part 1 PK only)	9	16	1	9	Day 1	Day 2 (first dose of MLN1117)	EOT	PFSFU/ OSFU
Fasting serum glucose (j, k)	X	X	X		X	X	X	X	X	X	X	
Fasting lipid profile	X						Day 1 of Cycle 4; Day 2 of Cycle 8 and every 4 cycles thereafter.					
HbA1c	X						Day 1 of Cycle 4; Day 2 of Cycle 8 and every 4 cycles thereafter.					
In-home daily fasting glucose monitoring (l)		See footnote l.										
Blood samples for PK (m)			X	X	X							
Plasma ctDNA (n)	X						Plasma will be collected on Day 1 of Cycles 3 and 5, and on Day 2 of Cycle 7 and every 2 cycles thereafter.					
Blood sample germline DNA (s)	X											
Banked tumor tissue or fresh biopsy sample (o)	X											
Disease Assessment												
Disease evaluation by RECIST, Version 1.1 (CT/MRI) (p)	X						Disease assessment to be conducted during Days 18-21 at the end of Cycles 2, 4, 6, and then every other cycle thereafter.					X q 12 wk
OS follow-up (OS and subsequent anticancer therapy) (q)												X q 12 wk

CxDx=Cycle x, Day x, CT=computed tomography, ctDNA=circulating tumor deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End of Treatment, HbA1c=glycosylated hemoglobin, IV=intravenous, MRI=magnetic resonance imaging, OS=overall survival, OSFU=overall survival follow-up, PD=progressive disease, PFS=progression-free survival, PFSFU=progression-free survival follow-up, PK=pharmacokinetic(s), PO=orally, RECIST=Response Evaluation Criteria in Solid Tumors.

(a) The Screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

(b) The informed consent form (ICF) may be signed more than 28 days prior to C1D1, but has to be signed before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

(c) A complete physical examination should be performed at screening and EOT. A symptom-directed physical examination should be performed on all other days as specified above.

[redacted]

(d) Vital signs measurements should be obtained at screening and on all other days as specified above. Vital signs include blood pressure, heart rate, and temperature.
(e) Single 12-lead ECGs will be obtained. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, then the ECG will be completed before the collection of the blood sample.
(f) See Section 9.5 for medications and procedures that are prohibited during the study and Section 9.6 for medications that should be used cautiously during the study.
(g) Only those serious adverse events (SAEs) that occur after the first dose of study drug will be collected in the electronic case report form; however, all SAEs occurring after consent will be reported. See Section 10.4.11.
(h) The study center staff will check the patient diary versus the patient's supply of MLN1117 tablets to assess compliance.
(i) A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on C1D1 with negative results available before the first dose of the study drug may be administered. A serum pregnancy test may also be performed within 3 days of dosing in place of the C1D1 urine test.
(j) Samples may be collected up to 3 days before the scheduled visit except for Cycle 1 Day 2. See Section 10.4.13.1 for the full hematology, coagulation, and clinical chemistry panels.
(k) Fasting serum glucose collected prior to MLN1117 dosing on every cycle, and at 2 hours post dosing only on Cycle 1 Day 2.
(l) Patients who experience on-study hyperglycemia will be given a glucometer to monitor their daily predose fasting blood glucose (FBG) levels at home and will be instructed to notify the investigator when the FBG is abnormal (ie, ≥140 mg/dL). Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. See Section 9.8.2 for further instruction.
(m) Patients in Part 1 (dose escalation) of the study will return to the clinic to have their 24-hour PK samples collected as specified in Table A.
Patients in Part 2 (dose expansion) of the study will return to the clinic to have their sparse PK samples collected as specified in Appendix Table C.
(n) A blood sample for plasma will be obtained at screening and every 2 cycles thereafter for evaluation of circulating tumor DNA.
(o) Collection of tumor tissue (banked) will be requested (Part 1) and required (Part 2) at screening as specified in Section 10.4.17. For banked tissue, the sample can be from either paraffin-embedded tumor block or unstained slides. If a paraffin-embedded tumor block or unstained slides are not available, the patient will be required to undergo a fresh tumor biopsy as specified in Section 10.4.18 (Part 2 only). The sample must be collected during screening before the first dose of study drug. Epstein-Barr virus (EBV) testing must be performed on all Part 2 (dose expansion) patients prior to randomization. In addition, tumor tissue will be analyzed and will be tested retrospectively for genetic mutations and amplifications.
(p) Response assessments will be performed on Days 18-21 at the end of treatment of Cycles 2, 4, 6, and then every 2 cycles thereafter until the patient discontinues study drug due to disease progression, unacceptable toxicity, or death. A CT scan with IV contrast of the chest, abdomen, and pelvis will be performed during screening (MRI of disease sites poorly imaged by CT is permitted; however, imaging modalities used for each disease site must be consistent throughout the study). If the patient has had an appropriate CT or MRI scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening. Patients who discontinue study drug treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study drug treatment, whichever occurs first.
(q) OS is to be assessed every 12 weeks until patient death or until 1 year after the last dose of study drug, whichever occurs first.
(r) Docetaxel may be administered after Cycle 6 if the investigator and sponsor determine that the patient would derive benefit from continued treatment.
(s) Blood samples will be collected at screening for extracting germline DNA to be used as a comparator for mutations in tumor samples.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) with permission of the project clinician for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician.**

Table A Serial Pharmacokinetic Sampling Schedule (Part 1)

Time Points	MLN1117+TAK-659 (a)		MLN1117+Alisertib (a)	MLN1117+Paclitaxel (b)	MLN1117+Docetaxel (b)
	Cycle 1				
	Day 1	Day 17	Cycle 1 Day 3	Cycle 1 Day 2	Cycle 1 Day 2
Predose (within 30 minutes before dosing)	X	X	X	X	X
0.5 hour (±5 min)	X	X	X	X	X
1 hour (±15 min)	X	X	X	X	X
2 hours (±15 min)	X	X	X	X	X
3 hours (±30 min)	X	X	X	X	X
4 hours (±45 min)	X	X	X	X	X
6 hours (±45 min)	X	X	X	X	X
8 hours (±1 hour)	X	X	X	X	X
24 hours (±1 hour)	X		X	X	X
Total samples	9	8	9	9	9

(a) Measure both MLN1117 and the combination agent.
(b) Measure MLN1117 only.

[redacted]

Table B Sparse Pharmacokinetic Sampling Schedule for MLN1117+TAK-659 and MLN1117+Alisertib Arms (Part 2)

Time points	MLN1117+TAK-659		MLN1117+Alisertib	
	Cycle 1 Day 8	Cycle 2 Day 15	Cycle 1 Day 8	Cycle 2 Day 15
Predose	X (a)		X (a)	
Approximately 1 to 2 hours postdose	X		X	
At time of clinic visit		X (b)		X (b)
Approximately 1 hour after last sample collection		X (b)		X (b)
Total samples	2	2	2	2

(a) The exact date and time of the previous dose of MLN1117, TAK-659, or alisertib will be recorded by the patient in the patient diary.
(b) To enable collection of a distribution of samples within the windows as defined in the table, patients are instructed to take their dose of study drug at home, early in the morning (before reporting for the scheduled study site visit) and to record the exact date/time of the dose in their patient diary.

[redacted]

Table C Sparse Pharmacokinetic Sampling Schedule for MLN1117+Paclitaxel and MLN1117+Docetaxel Arms (Part 2)

Time points	MLN1117+Paclitaxel		MLN1117+Docetaxel	
	Cycle 1 Day 2	Cycle 1 Day 9	Cycle 1 Day 2	Cycle 1 Day 9
Predose	X (a)		X (a)	
Approximately 1 to 2 hours postdose	X	X	X	X
Total samples	2	1	2	1

(a) The exact date/time of the previous dose of MLN1117 will be recorded by the patient in the patient diary.

[redacted]

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

[redacted]

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C 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. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix D Cockcroft-Gault Equation

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

OR

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[26]
F=1 for male patients.
F=0.85 for female patients.

[redacted]

Appendix E Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (a):
  - oral.
  - Intravaginal.
  - Transdermal.
- progestogen-only hormonal contraception associated with inhibition of ovulation (a):
  - oral.
  - Injectable.
  - implantable (b).
- intrauterine device (IUD) (b).
- intrauterine hormone-releasing system (IUS) (b).
- bilateral tubal occlusion (b).
- vasectomised partner (b,c).
- sexual abstinence (d).

Methods that are Considered Less Highly Effective

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

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- male or female condom with or without spermicide (e).
- cap, diaphragm or sponge with spermicide (e).

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

(a) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[redacted]

(b) Contraception methods that in the context of this guidance are considered to have low user dependency.

(c) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.

(d) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

(e) A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Appendix F Examples of Strong CYP3A Inhibitors and Inducers Prohibited During the Study

Drug / Agent Class	Examples (a)	Brand Name Example(s) (b)
Antifungal	Itraconazole	Sporanox, Onmel
	Ketoconazole	Nizoral, Xolegel, Extina
	Posaconazole	Noxafil
	Voriconazole	Vfend
Antibiotic	Clarithromycin	Biaxin
	Telithromycin	Ketek
Antimycobacterial	Rifabutin	Mycobutin
	Rifampin	Rifadin
	Rifapentine	Priftin
Antiepileptic	Carbamazepine	Tegretol, Equetro
	Phenobarbital	Luminal, Solfoton
	Phenytoin	Dilantin, Phenytek, Dilantin-125
	Primidone	Mysoline
Antidepressant	Nefazodone	Serzone
Calcium channel blocker	Mibefradil	Posicor
Antilipid	Avasimibe	Not available in the US
Vasopressin Antagonist	Conivaptan	Vaprisol
Herbal / Supplements / Food	Grapefruit	n/a
	Grapefruit juice	n/a
	St. John's wort	n/a
Antiviral	Boceprevir	Victrelis
	Telaprevir	Incivek, Incivo

HIV=human immunodeficiency virus, n/a=not applicable.
(a) Source: FDA website:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm (Anti-HIV drugs are not listed here because HIV+ patients are not eligible for enrollment in this study).
(b) Examples only; other brands may contain these active ingredients.

[redacted]

Appendix G Examples of P-Glycoprotein Inhibitors and Inducers Prohibited During the Study

Drug / Agent Class	Examples (a)	Brand Name Example(s) (b)
Antifungal	Itraconazole	Sporanox, Onmel
	Ketoconazole	Nizoral, Xolegel, Extina
Antibiotic	Azithromycin	Zithromax, Zmax, Z-Pak
	Clarithromycin	Biaxin
	Erythromycin	Eryc, Ery-Tab, E.E.S, Eryped, PCE
Antimycobacterial	Rifabutin	Mycobutin
	Rifampin	Rifadin
	Rifapentine	Priftin
Antiepileptic	Carbamazepine	Tegretol, Equetro
	Phenytoin	Dilantin, Phenytek, Dilantin-125
Immunosuppressant	Cyclosporine	Restasis, Neoral, Sandimmune
Cardiovascular medications (antiarrhymic, antiangina, antihypertensives, etc)	Amiodarone	Pacerone, Cordarone, Nexterone
	Captopril	Capoten
	Carvedilol	Coreg
	Diltiazem	Cardizem
	Dronedarone	Multaq
	Felodipine	Plendil
	Quinidine	Cardioquin, Quinidex Extentabs
	Ranolazine	Ranexa
	Verapamil	Calan, Verelan, Covera-HS
Antilipid	Avasimibe	Not available in the US
Vasopressin Antagonist	Conivaptan	Vaprisol
Antiplatelet	Ticagrelor	Brilinta
Herbal / Supplements	Quercetin	n/a
	St. John's Wort	n/a
Antiviral	Telaprevir	Incivek, Incivo

HIV=human immunodeficiency virus.
(a) Source: FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#PgpTransport (Anti-HIV drugs are not listed here because HIV+ patients are not eligible for enrollment in this study).
(b) Examples only; other brands may contain these active ingredients.

[redacted]

Appendix H Detailed Description of Amendments to Text

AMENDMENT 1 RATIONALE AND PURPOSE

The primary purposes of Amendment 1 were to update the protocol to include the TAK-659 dose as determined in Study C34001 and to change the protocol number. Contraception language was updated to align with the risk language in the updated consent form and to align with local labeling for paclitaxel and docetaxel. Other changes to certain procedures were incorporated, including changes to the Schedules of Events and some dose modification guidelines. In addition, administrative updates include incorporation of a development code alias for MLN1117 (TAK-117) and an update to the list of sponsor signatories. Grammatical and editorial changes were included for purposes of clarification and correction of inconsistencies. The following is a summary of the changes made in Amendment 1.

1. The TAK-659 dose as determined in Study C34001 was included.

   Justification: TAK-659 is a combination partner in 1 of the 4 cohorts in this study and the dose determination is for Cohort A (MLN1117+TAK-659).

2. The protocol number was changed from MLN1117-1003 to C032-6001.

   Justification: The label on bottles of study drug contain the protocol number. The original protocol number was MLN1117-1003. In this study with novel:novel drug combinations (ie, MLN1117 [also known as TAK-117] in combination with TAK-659 or alisertib), the appearance of Study MLN1117-1003 on the label may cause confusion for patients who have bottles containing TAK-659 or alisertib.

3. The development code TAK-117 as a synonym for MLN1117 was incorporated.

   Justification: Administrative update.

4. Sponsor signatories were updated.

   Justification: Administrative update.

5. Abbreviations introduced with Protocol Amendment 1, including the use of TAK-117 as a synonym for MLN1117, were updated.

   Justification: To define all abbreviations.

6. The Introduction and Background were updated.

   Justification: To include additional information on gastric cancer, updates based on recently available MLN1117 data, and updates based on recently available alisertib and TAK-659 safety data.

7. The rationale for the study was updated.

   Justification: To include additional information in the rationale for combining MLN1117 with the combinations partners (paclitaxel, docetaxel, alisertib, or TAK-659).

[redacted]

8. Objectives and endpoints were updated.

   Justification: Edits for purposes of clarification and alignment between objectives and endpoints.

9. Contraception language was updated, and language relating to donation of eggs and sperm has been added; an extended list of effective methods of contraception was added as an appendix.

   Justification: To align with updated risk language in the informed consent form, to align with paclitaxel and docetaxel labeling, and to provide an extended list of contraception methods that are considered to be effective.

10. Numbering of inclusion/exclusion criteria was updated to align with the EDC system.

    Justification: In the original protocol, numbering in each subsection of the inclusion and exclusion criteria restarted with numeral 1. The EDC system requires a unique number for each criterion within a section.

11. Exclusion criterion #12 regarding corticosteroid use was deleted.

    Justification: Oral corticosteroids used for approved conditions are not expected to interfere with the evaluation of safety or efficacy in patients with solid tumors.

12. Exclusion criteria relating to liver enzymes and serum lipase were updated.

    Justification: To include liver enzyme criteria consistent with the docetaxel label and to limit enrollment of patients with elevated lipase levels to the TAK-659 cohort.

13. The inclusion criterion relating to hemoglobin and the exclusion criterion relating to fasting serum glucose were updated.

    Justification: To provide clarification and more specific information relating to patient eligibility criteria.

14. Study drug administration was updated.

    Justification: To provide clarification of dosing for alisertib, approximately every 12 hours.

15. Definitions of dose-limiting toxicity were updated.

    Justification: To provide more specific definitions and further clarification with regard to dose-limiting toxicity to align DLT definitions with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

16. Dose escalation rules regarding adjustment of the fixed dose of the combination agent to a lower dose were updated.

    Justification: This update allows for adjustment to Dose Level -1 of the combination agent in the event that Dose Level 1 is above the MTD.

17. Dose escalation of MLN1117 above 900 mg will not be allowed.

    Justification: 900 mg MLN1117 is considered the MTD of MLN1117 as a single agent.

[redacted]

18. The dose-reduction levels table was updated.

    Justification: Based on known TAK-659 dose, inclusion of dose reduction levels for TAK-659.

19. Dose modification guidelines for toxicities, including tables, were updated.

    Justification: To provide additional guidance, including clarification and simplification, on dose modification guidelines for toxicities.

20. Management of hyperglycemia was updated.

    Justification: To provide clarification and additional guidance.

21. The timing of antacid ingestion after study drug dosing was updated.

    Justification: For consistency with timing of histamine-2 antagonist ingestion after study drug dosing.

22. Study drug storage information for TAK-659 was updated.

    Justification: To provide additional guidance.

23. Additional laboratory evaluations (coagulation, serum lipase, serum amylase) were included.

    Justification: Patient safety.

24. Study-specific committees and reference to a Cohort Management Plan document were added.

    Justification: Patient safety oversight and to provide further guidance on the process to drive allocation of patients in Part 1.

25. A blood sample for germline DNA was added.

    Justification: Comparator for mutations detected in tumor samples.

26. Crossover to a different treatment arm in Part 2 was deleted.

    Justification: Crossover to a different treatment arm will not be allowed.

27. Recommended phase 2 dose (RP2D) was revised to recommended Part 2 dose in sections of the protocol relating to Part 1.

    Justification: In sections of the protocol relating to Part 1, the determined recommended dose is referred to as the recommended Part 2 dose rather than the RP2D; the RP2D will be determined at the end of the study.

28. The duration of treatment was updated.

    Justification: To clarify the maximum duration of treatment and exceptions to the maximum duration of treatment with MLN1117 or the combination partners.

29. The Duration of Study section was updated.

    Justification: To remove redundancy with other sections and better align with the section heading.

[redacted]

30. Disease assessment with regard to collection of electronic images of scans was updated.

    Justification: To clarify the central collection of scans; all scans are collected centrally regardless of antitumor response.

31. The Randomization and Stratification section was updated with additional information.

    Justification: To provide further details.

32. Serious adverse event definition and analysis sections were updated.

    Justification: To provide additional information and updates.

33. The statement regarding the requirement for completed electronic case report forms was corrected.

    Justification: To correct an erroneous statement.

34. The Schedule of Events for Cohort C (MLN1117+paclitaxel) was revised to remove scheduled procedures on Cycle 1 Day 9 (except for PK sampling) and to remove the Cycle 1 Day 16 visit.

    Justification: There are clinic visits scheduled on Cycle 1 Day 8 and Cycle 1 Day 15; by removing the procedures as stated, this relieves the patient from clinic procedures on 2 consecutive days.

35. Revisions, updates, and edits were made for purposes of clarification and consistency.

36. Typographical errors, punctuation, grammar, and formatting were corrected.

AMENDMENT 2 SUMMARY OF CHANGES

This summary describes the changes made in reference to Protocol Incorporating Amendment No. 2.

Page 45, Section 9.2, Definitions of Dose-Limiting Toxicity

Existing Text: Toxicity will be evaluated according to the NCI CTCAE, Version 4.03. These criteria are provided in the Study Manual. DLT will be defined as any of the following events occurring during Cycle 1 in Part 1 that are considered by the investigator to be at least possibly related to ~~therapy with~~ MLN1117 ~~when administered in combination with~~ TAK-659, alisertib, paclitaxel, or docetaxel.

Revised Text: Toxicity will be evaluated according to the NCI CTCAE, Version 4.03. These criteria are provided in the Study Manual. DLT will be defined as any of the following events occurring during Cycle 1 in Part 1 that are considered by the investigator to be at least possibly related to **either or both of the study drugs (**MLN1117**,** TAK-659, alisertib, paclitaxel, or docetaxel**) in an assigned combination regimen:**

Rationale for Amendment: To ensure that the DLT assessments reflect the toxicity of the administered combination regimens and not exclusively a single agent within the combination.

Page 45, Section 9.2, Definitions of Dose-Limiting Toxicity

- **Existing Text:** Grade 3 or greater nonhematologic toxicity with the following exceptions:
  - Grade 3 arthralgia/myalgia.
  - Grade 3 fatigue that lasts less than 1 week.
  - ≥Grade 3 nausea and/or emesis that can be controlled to ≤Grade 1 or baseline in 7 days with the use of optimal antiemetic prophylaxis (defined as an antiemetic regimen that employs both a 5-HT antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - ≥Grade 3 diarrhea that can be controlled to ≤Grade 1 or baseline in 7 days with optimal supportive therapy.
- **Revised Text:** Grade 3 or greater nonhematologic toxicity with the following exceptions:
  - Grade 3 arthralgia/myalgia.
  - Grade 3 fatigue that lasts less than 1 week.
  - Grade 3 nausea and/or emesis that can be controlled to ≤Grade 1 or baseline in 7 days with the use of optimal antiemetic prophylaxis (defined as an antiemetic regimen that employs both a 5-HT antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - Grade 3 diarrhea that can be controlled to ≤Grade 1 or baseline in 7 days with optimal supportive therapy.

Rationale for Amendment: Grade 4 events are life-threatening per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 and, therefore, are always DLTs.

Page 82, Section 10.4.17, Banked Tumor Specimen Measurements

Existing Text: An archival ~~or fresh~~ tumor ~~biopsy~~ sample needs to be available for enrollment in Part 2. Archival tumor tissue will be collected from Part 1 patients whenever possible. [redacted]

Revised Text: An archival tumor **tissue** sample needs to be available for enrollment in Part 2. Archival tumor tissue will be collected from Part 1 patients whenever possible. [redacted]

Rationale for Amendment: To provide clarification.

Page 82, Section 10.4.18, Tumor Biopsies

Existing Text: For Part 2, access to a tumor biopsy is required. If a patient does not have archived tumor tissue for evaluation of the EBV status and analysis of biomarkers, a new fresh pretreatment biopsy is required. ~~This new biopsy must be obtained at least 2 days after the last dose of any prior anticancer therapy and within 14 days before the first dose of study drug treatment.~~ Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an activated partial thromboplastin time (aPTT) and prothrombin time (PT) within the normal range; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible.

Revised Text: For Part 2, access to a tumor biopsy is required. If a patient does not have archived tumor tissue for evaluation of the EBV status and analysis of biomarkers, a new fresh pretreatment biopsy is required. Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an activated partial thromboplastin time (aPTT) and prothrombin time (PT) within the normal range; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. The tumor biopsy procedure

will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible.

Rationale for Amendment: To allow for flexibility in obtaining fresh pretreatment biopsies.

Page 82, Section 10.4.18, Tumor Biopsies

Existing Text: For Part 2, access to a tumor ~~biopsy~~ is required. If a patient does not have archived tumor tissue for evaluation of the EBV status and analysis of biomarkers, a new fresh pretreatment biopsy is required. This new biopsy must be obtained at least 2 days after the last dose of any prior anticancer therapy and within 14 days before the first dose of study drug treatment. Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an activated partial thromboplastin time (aPTT) and prothrombin time (PT) within the normal range; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible.

Revised Text: For Part 2, access to a tumor **tissue sample** is required. If a patient does not have archived tumor tissue for evaluation of the EBV status and analysis of biomarkers, a new fresh pretreatment biopsy is required. Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an activated partial thromboplastin time (aPTT) and prothrombin time (PT) within the normal range; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible.

Rationale for Amendment: To provide clarification.

Page: Various, Section: Various

Existing Text: Existing text is not listed individually.

Revised Text: These changes are not listed individually.

Rationale for Amendment: Correct typographical errors, punctuation, grammar, and formatting.

Amendment 2 – An Umbrella Study to Evaluate MLN1117 in Combination with Taxanes (Docetaxel or Paclitaxel) and Other Investigational Anticancer Agents for the Treatment of Patients with Previously Treated Advanced and Metastatic Gastric and Gastroesophageal Adenocarcinoma

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical Approval	30-Jan-2016 08:47
PPD	Clinical Pharmacology Approval	01-Feb-2016 13:53
PPD	Biostatistics Approval	01-Feb-2016 14:47
PPD	Clinical Approval	01-Feb-2016 17:45