Title: A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of Single-Agent MLN0128 and the Combination of MLN0128+MLN1117 Compared With Everolimus in the Treatment of Adult Patients With Advanced or Metastatic Clear-Cell Renal Cell Carcinoma That Has Progressed on Vascular Endothelial Growth Factor-Targeted Therapy

NCT Number: NCT02724020

Protocol Approve Date: 03-December-2018

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

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PROTOCOL

A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of Single-Agent MLN0128 and the Combination of MLN0128+MLN1117 Compared With Everolimus in the Treatment of Adult Patients With Advanced or Metastatic Clear-Cell Renal Cell Carcinoma That Has Progressed on Vascular Endothelial Growth Factor-Targeted Therapy

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
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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: C31005

IND Number: 126,347 **EudraCT Number:** 2015-002133-22

Compound: MLN0128, MLN1117

Date: 03-December-2018 **Amendment Number:** 10 (France)

Amendment History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
22 May 2015	Initial Protocol	Not applicable	Global
09 February 2016	01	Nonsubstantial	Global
15 September 2016	02	Nonsubstantial	France
01 December 2016	03	Substantial	France
17 April 2017	04	Substantial	Global
17 April 2017	05	Substantial	France
03 October 2017	06	Substantial	Global
02 October 2017	07	Substantial	France
26-October-2017	08	Substantial	Hungary
03-December-2018	09	Substantial	Global
03 December-2018	10	Substantial	France

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

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, as applicable) can be found on the signature page.

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

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package inserts, 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 11.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B, Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 10 Summary of Changes

Rationale for Amendment 10

This document describes the changes in reference to the protocol incorporating Amendment No. 10. The primary purpose of this amendment is to define study closure, remove long-term follow-up, remove the option for cross-over treatment, and add the option of a Post-Trial Access (PTA) program.

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

For specific descriptions of text changes and where the changes are located, see Appendix L.

Changes in Amendment 10

1. Removed long-term follow-up, the option for cross-over treatment from Arm A to Arm B or Arm C, and added the option for patients to transfer to a Post-Trial Access (PTA) program.
2. Study closure was defined as when the last patient discontinues treatment.
3. A new section was added (10.10) detailing the PTA program.
4. Modified the exclusion criterion relating to proton-pump inhibitors (PPIs).
5. Revised the restrictions on concomitant use of PPIs.
6. Physical examinations after Screening were changed to symptom-directed physical examinations.
7. The requirement for a confirmatory scan 4 weeks from the previous scan for patients with a complete response (CR) or partial response (PR) was removed.
8. A recommendation was added for radiographic assessment every 6 months after 12 cycles of treatment.
9. The requirement for weight to be measured at Day 15 of Cycles 1 and 2 was removed.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc	**Compound:** MLN0128, MLN1117	
Title of Protocol: A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of Single-Agent MLN0128 and the Combination of MLN0128+MLN1117 Compared With Everolimus in the Treatment of Adult Patients With Advanced or Metastatic Clear-Cell Renal Cell Carcinoma That Has Progressed on Vascular Endothelial Growth Factor-Targeted Therapy	**IND No.:** 126,347	**EudraCT No.:** 2015-002133-22
Study Number: C31005	**Phase:** 2	
Study Design: This phase 2, open-label, randomized, 3-arm study is designed to evaluate the efficacy and safety of single-agent MLN0128 and the combination of MLN0128 and MLN1117 compared with single-agent everolimus in the treatment of patients with metastatic clear-cell renal cell carcinoma (mccRCC) that has progressed on vascular endothelial growth factor (VEGF)-targeted therapy. Patients who meet the eligibility criteria will be stratified according to the number of prior lines of therapy (1, >1 prior line) and the International Metastatic Renal Cell Carcinoma Database Consortium risk category (favorable, intermediate, or poor) and will be randomized at a ratio of 1:1:1 to one of 3 treatment groups: • Arm A: single-agent everolimus. • Arm B: single-agent MLN0128. • Arm C: combination of MLN0128+MLN1117. Safety assessments (which include vital signs, hematology, serum chemistry, and urinalysis) will be performed every 2 weeks for the first two 28-day cycles and then at the beginning of each subsequent cycle thereafter.		
Primary Objectives: • To compare the efficacy of single-agent MLN0128 versus single-agent everolimus in patients with mccRCC. • To compare the efficacy of the combination of MLN0128+MLN1117 versus single-agent everolimus in patients with mccRCC.		
Secondary Objectives: • To assess the safety and tolerability of MLN0128 and MLN0128+MLN1117. • To compare the efficacy of the combination of MLN0128+MLN1117 versus single-agent MLN0128 in patients with mccRCC. • To evaluate the efficacy (endpoints other than progression-free survival [PFS]; ie, overall survival [OS], time-to-progression [TTP], objective response rate [ORR], and clinical benefit rate [CBR]) among the 3 treatment groups. • To collect plasma concentration-time data with sparse pharmacokinetic (PK) sampling to contribute to future population PK analysis. **Quality of Life Objective:** • To assess the health-related quality of life and symptoms as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-Related Symptoms questionnaire among the 3 treatment groups.		
Subject Population: Patients aged ≥18 years with mccRCC that has progressed on VEGF-targeted therapy		
Number of Subjects: Approximately 189 patients • Arm A: everolimus; n=approximately 63.	**Number of Sites:** Approximately 60-70 sites in North America and Europe	

• Arm B: MLN0128; n=approximately 63. • Arm C: MLN0128+MLN1117; n=approximately 63.	
Dose Level(s): • Arm A: everolimus, 10 mg once daily (QD; every day of a 28-day treatment cycle). • Arm B: MLN0128, 30 mg every week on Days 1, 8, 15, and 22 of a 28-day treatment cycle. • Arm C: MLN0128 4 mg+MLN1117 200 mg, both QD×3 days per week (on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle).	**Route of Administration:** • MLN0128: oral. • MLN1117: oral. • Everolimus: oral.
Duration of Treatment: Patients will receive MLN0128, MLN0128+MLN1117, or everolimus until they experience disease progression or unacceptable toxicity, withdraw consent, die, or transfer to the Post-Trial Access (PTA) program. The maximum duration of treatment will be 24 months.	**Period of Evaluation:** The study will be closed when the last patient discontinues study treatment.
Main Criteria for Inclusion: Adult patients with histologically confirmed renal cell carcinoma with a clear-cell component, measurable disease per RECIST version 1.1, adequate bone marrow reserve and renal and hepatic function based on minimum laboratory criteria, Karnofsky performance status of 70% or higher, and life expectancy of at least 3 months. Eligible patients must have received at least one prior line of VEGF-targeted therapy and must have had radiographic evidence of progressive disease either on or within 6 months of stopping their most recent systemic therapy for advanced mccRCC, and may have received up to 4 total prior lines of therapy.	
Main Criteria for Exclusion: Patients who have central nervous system metastases, uncontrolled comorbidities such as pulmonary disease or infection that might compromise the patient's participation in the study, and women who are either breast-feeding or pregnant, will be excluded.	
Main Criteria for Evaluation and Analyses: The primary endpoint of the study is PFS. The secondary endpoints are the incidence of treatment-emergent adverse events, OS, TTP, ORR (complete response [CR]+partial response [PR] per RECIST version 1.1), CBR (defined as CR+PR+stable disease[SD]) with SD of any duration, and CBR with SD duration of at least 4 months.	
Statistical Considerations: The primary endpoint of the study is PFS, defined as the time from the date of randomization to the date of first documentation of disease progression or death due to any cause, whichever occurs first. For a patient whose disease has not progressed and is last known to be alive, PFS will be censored at the last response assessment that is SD or better. The primary efficacy analysis will be based on the full analysis set. The Kaplan-Meier method will be used to analyze the distribution of PFS for each treatment arm. Kaplan-Meier survival curves; the 25th, 50th (median), and 75th percentiles along with associated 2-sided 95% CIs; hazard ratio along with associated 95% CI; and Kaplan-Meier estimates at relevant time points will be presented. The primary hypothesis is to be tested at the 0.15 significance level (2-sided). The p-values from a stratified log-rank test and hazard ratios and will be presented for each pair-wise comparison. Secondary efficacy endpoints include OS, ORR, TTP, CBR (CR+PR+SD of any duration), and CBR with SD duration of at least 4 months. OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed using similar methods as the primary endpoint of PFS in the full analysis set.	

ORR is defined as the proportion of patients who achieve a best response of CR or PR. CBR is defined as the proportion of patients who achieve a best response of CR, PR, or SD. CBR will also be presented for a best response of CR, PR, and SD of at least 4 months. A stratified Cochran-Mantel-Haenszel test will be used to compare ORR and CBR between treatment arms. The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each pair-wise comparison.

TTP is defined as the time from the date of randomization to the date of first documentation of progression. For a patient whose disease has not progressed, TTP will be censored at the last response assessment that is SD or better. TTP will be analyzed using similar methods as the primary endpoint of PFS in the full analysis set.

Sample Size Justification:

Approximately 189 patients will be enrolled in the 3 treatment arms.

The primary efficacy endpoint is PFS. Assuming that the median PFS is 5 months for everolimus and that MLN0128 (either as a single agent or in combination with MLN1117) can improve the median PFS to 8 months (hazard ratio of 0.625), then a total of 95 PFS events are needed for each pair-wise comparison, and approximately 63 patients are required for each treatment arm. The calculations are based on a power of 80%, 2-sided alpha of 15%, and a dropout rate of 10% due to either lost to follow-up or withdrawal of consent.

The sample size for the study assumes the total accrual will be approximately 14 months, where 10% of the patients are enrolled within the first 3 months and 40% are enrolled at the end of 7 months. The final analysis for the pair-wise comparisons of PFS between single-agent MLN0128 and everolimus and between the combination of MLN0128+MLN1117 and everolimus will occur approximately 9 months after the last patient is randomized.

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 or Investigators 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

4E-BP1	eukaryotic translation initiation factor 4E-binding protein 1
AE	adverse event
AKT	serine/threonine-specific protein kinase (also known as protein kinase B)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End-of-Treatment (visit)
FBG	fasting blood glucose
FDA	Food and Drug Administration
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms
GCP	Good Clinical Practice
GI	gastrointestinal
HbA1c	glycosylated hemoglobin, hemoglobin A1c
HDPE	high-density polypropylene
HIF	hypoxia-inducible factor
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous; intravenously
IXRS	interactive voice and/or web response system
mccRCC	metastatic clear-cell renal cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc and its affiliates
MLN0128	also known as TAK-228

MLN1117	also known as TAK-117
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mechanistic (or mammalian) target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OCT1	organic cation transporter protein 1
OCT2	organic cation transporter protein 2
ORR	objective response rate
OS	overall survival
p-	phosphorylated
PCP	*Pneumocystis carinii* pneumonia
PDGF	platelet-derived growth factor
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PI3Kα	phosphoinositide 3-kinase alpha subunit
PIK3CA	phosphoinositide-3-kinase, catalytic alpha polypeptide
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
PRO	patient-reported outcomes
PTA	Post-Trial Access
PTE	pretreatment event
PTEN	phosphatase and tensin homolog
QD	*quaque die*; each day; once daily
QD×3 QW	once daily for 3 days each week
QOL	quality of life
QW	every week
QTc	rate-corrected QT interval (msec)
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
S473	serine 473
S6K	ribosomal protein S6 kinase
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TAK-117	MLN01117
TAK-228	MLN0128

TEAE	treatment-emergent adverse event
TORC1	mammalian (or mechanistic) target of rapamycin complex 1
TORC2	mammalian (or mechanistic) target of rapamycin complex 2
TTP	time-to-progression
ULN	upper limit of normal (range)
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
VHL	von Hippel-Lindau
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Kidney cancer is the twelfth most common cancer world-wide, with an estimated 338,000 new cases based on 2012 global data [1]. The incidence of kidney cancer is higher in men than in women, with 214,000 new cases in men and 124,000 new cases in women. Geographically, the highest incidence rates are in Northern and Eastern Europe, North America, and Australia [1,2]. However, the overall incidence rates have been increasing over the last 3 decades [3]. More than 90% of kidney cancers are renal cell carcinoma (RCC), of which 80% have a clear-cell morphology [4].

4.1.1 RCC

RCC is a highly vascularized tumor that is refractory to chemotherapy and can be treated with molecularly targeted antiangiogenic compounds, including tyrosine kinase inhibitors that act on the vascular endothelial growth factor (VEGF) receptor (such as sunitinib, sorafenib, axitinib, and pazopanib), anti-VEGF antibody (bevacizumab), and rapalogs (temsirolimus and everolimus).

Approximately 80% to 90% of clear-cell carcinomas have either biallelic mutation or inactivation of the von Hippel-Lindau (VHL) gene, which regulates hypoxia-inducible factor (HIF)-1α and HIF-2α transcription factors that are involved in the hypoxia response [5-8]. As part of the hypoxic response, the HIF-1α and HIF-2α transcription factors lead to an increase in the expression of angiogenic growth factors, such as VEGF, platelet-derived growth factor-β (PDGF-β), transforming growth factor-α, and angiopoietin-1 [5,7,8].

When oxygen is restored, the VHL protein forms a multiprotein complex that is involved in the ubiquitination and subsequent proteasomal degradation of the HIF transcription factors. When VHL is absent, the angiogenic growth factors are expressed constitutively in the absence of hypoxia.

Therapy has focused on the growth factor (eg, VEGF, PDGF) and mechanistic (or mammalian) target of rapamycin (mTOR) signaling pathways. Tyrosine kinase inhibitors that inhibit angiogenic growth factor receptors, such as VEGF and PDGF receptors, and anti-VEGF antibody (bevacizumab) are approved for first-line therapy in RCC; however, development of resistance to VEGF-targeted therapy occurs almost invariably.

The mTOR Pathway as a Therapeutic Target in RCC

The mTOR pathway is another therapeutic target in RCC. The mTOR serine/threonine kinase has a central role in regulating cellular growth and metabolism in response to external environmental factors [9,10]. The mTOR kinase binds with other proteins to form 2 distinct multiprotein complexes, mTOR complex 1 (TORC1) and mTOR complex 2 (TORC2). The TORC1 complex is stimulated by growth factors and amino acids, and regulates cell growth by controlling the activity of the ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) [11]. The TORC2 complex is activated by growth factors, and promotes cell survival, proliferation, and actin cytoskeleton organization by phosphorylating and activating

kinases, such as serine/threonine-specific protein kinase (AKT, also known as protein kinase B), which is a regulator of apoptosis [12,13].

Two major classes of mTOR inhibitors are under development: allosteric inhibitors and adenosine triphosphate (ATP)-competitive inhibitors. The first-generation, or allosteric, inhibitors include rapamycin and the related analogs or rapalogs temsirolimus, everolimus, and ridaforolimus. The rapalogs effectively inhibit phosphorylation of S6K, but only partially inhibit the phosphorylation of 4E-BP1, which regulates cap-dependent translation of transcripts for cell survival, proliferation, and angiogenesis [9,10]. Thus, rapamycin and the rapalogs are only partial inhibitors of TORC1 [9,10].

The ATP-competitive inhibitors (also known as mTOR kinase inhibitors or TORKinibs), such as MLN0128, bind to the catalytic domain of mTOR. Thus, these agents inhibit both TORC1 and TORC2 complexes, including the rapamycin-insensitive or -resistant actions of TORC1, such as phosphorylation of 4E-BP1 [14-17].

Resistance to Rapalogs

The rapalogs temsirolimus and everolimus have been approved by the United States (US) Food and Drug Administration (FDA) as monotherapy for patients with advanced RCC. However, resistance to single-agent rapalog therapy occurs frequently and may be related to either incomplete inhibition of the targeted pathway (such as phosphorylation of 4E-BP1) or the loss of S6K-mediated feedback inhibition of growth-factor receptor signaling, leading to paradoxic hyperactive signaling. The normal feedback loop involves activated S6K, which phosphorylates and inactivates insulin-receptor substrate-1 and inhibits signaling through the phosphoinositide 3-kinase (PI3K) pathway [13,18]. In the presence of rapalogs, the feedback loop is abrogated, leading to continued PI3K signaling, TORC2 activation, and subsequent phosphorylation of AKT at threonine 308 and serine 473 (S473), which markedly enhances the activity of AKT [9,10,13,18]. This leads to continued signaling from the receptor through the PI3K pathway, TORC2, and AKT, leading to cell survival and proliferation.

The loss of feedback inhibition by rapalogs has been demonstrated in clinical trials. In an analysis of either paired fresh tumor samples or skin biopsies obtained from 55 patients who received different doses of everolimus, either daily or weekly in a phase 1 trial, everolimus inhibited TORC1 in a dose- and schedule-dependent manner, with near complete inhibition of S6K [19]. Half of the paired tumor samples had a posttreatment increase in the phosphorylation of AKT at S473 [19]. These results provide direct evidence that loss of S6K feedback and subsequent PI3K/TORC2-induced activation of AKT occurs commonly in patients with nonhematologic tumors receiving single-agent everolimus.

The rapalog everolimus is an allosteric inhibitor of TORC1. In a phase 3 study of single-agent everolimus in patients whose VEGF-targeted therapy had failed, single-agent everolimus prolonged median progression-free survival (PFS) by approximately 3 months compared with patients who received placebo and best supportive care (median PFS 4.9 months vs 1.9 months) [20]. The less-than-expected anticancer activity of single-agent rapalogs may be due to incomplete

inhibition of TORC1 actions, such as 4E-BP1, or the loss of feedback inhibition of the signaling pathway mediated by S6 kinase following pharmacologic inhibition of TORC1.

4.1.2 Study Drugs MLN0128 and MLN1117

MLN0128

MLN0128 (also known as TAK-228) is a potent and selective catalytic mTOR (TORC1/2) inhibitor that has the potential to improve upon everolimus treatment response in metastatic clear-cell RCC (mccRCC) through a more complete inhibition of TORC1 signaling (S6 and 4E-BP1) and through inhibition of TORC2 substrates, such as AKT. This could lead to a more profound block of the angiogenic growth and survival signaling than that achieved with rapalogs.

Clinical Experience With MLN0128

Single-agent MLN0128 is in clinical development with 3 phase 1 studies in patients with advanced non-hematologic tumors (Studies INK128-001, MLN0128-1004, and C31002). In addition, MLN0128 is being investigated in combination with paclitaxel, with or without trastuzumab, in a phase 1 study in patients with advanced solid tumors (INK128-003).

Milled MLN0128 is being investigated either as a single agent or in combination with paclitaxel in an additional phase 1 study in patients with advanced solid tumors (Study MLN0128-1004) and in a phase 1/2 study in patients with advanced estrogen receptor-positive, human epidermal growth factor receptor-2 negative breast cancer (Study C31001).

The most common treatment-emergent adverse events (TEAEs) observed with MLN0128 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual mTORC1/2 inhibitors. The TEAEs observed across the MLN0128 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite.

MLN0128 has been shown to have antitumor activity against RCC in a murine xenograft model. In addition, preliminary clinical data from a tumor-specific expansion cohort in Study INK128-001 suggests that MLN0128 has antitumor activity in patients with RCC.

Further details are presented in the current edition of the MLN0128 Investigator's Brochure (IB).

MLN1117 in Combination With MLN0128

MLN1117 (also known as TAK-117) is a potent and highly selective small-molecule inhibitor of the class I PI3K alpha subunit (PI3Kα) isoform. PI3Kα is activated by upstream receptor tyrosine kinases such as epidermal growth factor receptors, human epidermal growth factor receptor-2, insulin-like growth factor-1 receptor, and insulin receptors, and possibly by activated Ras.

The addition of the PI3Kα inhibitor MLN1117 to MLN0128 should counteract the reactivation of this pathway and enhance MLN0128 activity. This is supported by indirect evidence from nonclinical studies with NVP-BEZ235, a dual PI3K/mTOR inhibitor, and rapamycin in RCC cell lines and murine xenograft models. In these investigations, NVP-BEZ235 was associated with

more profound reduction in tumor size and more complete inhibition of phosphorylation of TORC1/2 and PI3K substrates, including AKT, eukaryotic translation initiation factor 4E, and 4E-BP1, than rapamycin [21]. Thus, the combination of MLN0128 and milled MLN1117 has the potential to improve MLN0128 treatment response in mccRCC through a more complete and prolonged inhibition of this signaling pathway.

Clinical Experience of MLN1117 in Combination With MLN0128

MLN1117 is in clinical development for the treatment of advanced non-hematologic tumors, as a single agent (Study INK1117-001) and in combination (Study C32001). These studies have been designed to investigate the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of MLN1117, either as a single agent or in combination with MLN0128.

Potential overlapping toxicities associated with MLN0128 and MLN1117, and the identified and potential risks of both drugs, including data from nonclinical and clinical studies for each product, have been reviewed. More detailed information on the identified and potential risks of both drugs is included in the individual, single-agent IBs. Class effects of mTOR inhibitors (for MLN0128) and PI3K inhibitors (for MLN1117) have also been considered. Potential overlapping toxicities for both agents include:

- Dermatologic disorders (pruritus, rash).
- Gastrointestinal (GI) disorders (diarrhea, mucosal inflammation, nausea, stomatitis, vomiting).
- Generalized disorders (anorexia, asthenia, decreased appetite, fatigue).
- Hematologic disorders (lymphoid, bone marrow depletion).
- Metabolic disorders (decreased blood chloride, hypercholesterolemia, hyperglycemia).

On the basis of current clinical experience, and the previous list of potential overlapping toxicities, hyperglycemia, diarrhea, nausea, vomiting, fatigue, and rash are the most anticipated adverse events (AEs) associated with the MLN0128+MLN1117 combination regimen. These events are expected to be manageable.

Further details are presented in the current edition of the MLN0128, MLN0128+MLN1117, and MLN1117 IBs.

Preliminary PK of MLN0128

The PK parameters measured for unmilled MLN0128 active pharmaceutical ingredient in the phase 1 clinical studies have been generally consistent across a range of doses and multiple schedules. MLN0128 has shown linear PK and fast oral absorption with first time of occurrence of maximum (peak) concentration occurring between 1 and 4 hours after a single dose. The mean half-life of MLN0128 is approximately 8 hours, and no accumulation has been observed in plasma after repeat daily dosing.

4.2 Rationale for the Proposed Study

A TORC1/2 inhibitor would be expected to provide more complete inhibition of the mTOR pathway than a rapalog, and the combination of a PI3Kα inhibitor with a TORC1/2 inhibitor would be expected to provide more robust inhibition of the mTOR and growth factor signaling pathways than either agent alone. This randomized, open-label, 3-arm investigation of MLN0128, MLN0128+MLN1117, and everolimus will test the hypothesis that TORC1/2 inhibition, either with or without additional PI3Kα inhibition, will provide better efficacy compared with single-agent rapalog inhibition of TORC1 in patients with mccRCC and progressive disease after VEGF-targeted therapy.

4.2.1 Rationale for the Doses and Schedule in Arm B

The selected dose and schedule for Arm B of 30 mg MLN0128 every week (QW) is based on the findings from 2 studies: Study INK128-001 and Study MLN0128-1004.

Study INK128-001was the first-in-human study of MLN0128. Study INK128-001 was an open-label study designed to determine the maximum tolerated dose (MTD) and to identify dose-limiting toxicities (DLTs) for oral administration of single-agent unmilled MLN0128, and to characterize the safety and tolerability of escalating doses of MLN0128 in patients with advanced solid tumors. In this study, 116 patients with advanced solid tumors received single-agent MLN0128 (2-40 mg via 4 dosing schedules) in the dose escalation phase.

Doses of 40 mg QW, 30 mg QW, and 5 mg once daily (QD) were further evaluated in an additional 82 patients in the expansion phase.

Improved tolerability, including a reduced frequency of TEAEs leading to dose interruptions and modifications, respectively (5 mg QD [26% and 67%] vs 30 mg QW [24% and 41%] vs 40 mg QW [19% and 77%] as of a data cut on 09 December 2015), and longer duration of clinical benefit favored 30 mg QW dosing as a recommended phase 2 dose (RP2D) and schedule for further development.

With the introduction of milled MLN0128, the recommended dose to be used in Arm B of this study (30 mg milled MLN0128 QW) was further confirmed in Study MLN0128-1004 (Table 4.a). A total of 14 patients were enrolled and assigned, sequentially, to 2 QW dosing cohorts. PK, safety, and tolerability were assessed.

Table 4.a DLT Observed With Weekly MLN0128 in Study MLN0128-1004

Dose of Milled MLN0128	Number of Evaluable Patients	DLTs Observed in Cycle 1
20 mg QW	6	None
30 mg QW	6	None

As none of the patients in either dose cohort experienced DLT in Cycle 1, a dose of 30 mg MLN0128 QW was selected for further development. No clinically meaningful differences in the

PK of MLN0128 were noted between the unmilled MLN0128 (Study INK128-001) and milled MLN0128 (Study MLN0128-1004) when given QW.

4.2.2 Rationale for the Doses and Schedule in Arm C

The dose and schedule selected for Arm C of 4 mg MLN0128 plus 200 mg of MLN1117 (both once daily for 3 days each week [QD×3 QW]) are based on the results of Study C32001 conducted under IND 117,524. Study C32001 is an ongoing, open-label study designed to determine the MTD and DLTs for oral administration of milled MLN0128 given in combination with MLN1117 and was designed to characterize the safety and tolerability of escalating doses of MLN0128 and/or MLN1117 in patients with advanced solid tumors. The study featured a dose-escalation phase evaluating 3 dosing schedules. A favorable tolerability profile was observed when increasing doses of MLN0128 (3 to 8 mg) were administered with a fixed dose of MLN1117 (both given QD×3 QW). The MTD for MLN0128 in combination with MLN1117 both given QD×3 QW was 6 mg MLN0128+200 mg MLN1117 (Table 4.b).

Table 4.b DLT Observed With MLN0128 Plus MLN1117 (3 Days Per Week) in Study C32001

Dose of Milled MLN0128+MLN1117	Number of Evaluable Patients	DLTs Observed in Cycle 1
6 mg+200 mg QD×3 QW	6	1 patient experienced DLT of aspartate aminotransferase/ alanine aminotransferase elevation)
4 mg+200 mg QD×3 QW	8	None

While both combination dose levels were considered safe on the basis of 3+3 rules, the lower dose level of 4 mg+200 mg QD×3 QW was chosen as the RP2D for milled MLN0128+MLN1117 for further development.

The mechanistic justification for comparing the effectiveness of either single-agent MLN0128 or the combination of MLN0128 and MLN1117 with that of everolimus in patients with RCC is outlined in detail in Section 7.0.

Briefly, a TORC1/2 inhibitor like MLN0128 would be expected to provide more complete inhibition of the mTOR pathway than a rapalog (eg, everolimus as an allosteric TORC1 inhibitor), and the combination of a PI3Kα inhibitor (MLN1117) with a TORC1/2 inhibitor (MLN0128) would be expected to provide more robust/sustained inhibition of the mTOR and growth factor signaling pathways than either agent alone. This randomized, open-label, 3-arm investigation of MLN0128, MLN0128+MLN1117, and everolimus will test the hypothesis that TORC1/2 inhibition, either with or without additional PI3Kα inhibition, will provide better efficacy compared with single-agent rapalog inhibition of TORC1 in patients with mccRCC and progressive disease after VEGF-targeted therapy.

4.3 Potential Risks and Benefits

The most common TEAEs observed with MLN0128 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual mTORC1/2 inhibitors. The TEAEs observed across the MLN0128 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite.

Potential overlapping toxicities associated with MLN0128 and MLN1117 and the identified and potential risks of both drugs, including data from nonclinical and clinical studies for each product, have been reviewed. More detailed information on the identified and potential risks of both drugs is included in the individual single-agent IBs. Class effects of mTOR inhibitors (for MLN0128) and PI3K inhibitors (for MLN1117) have also been considered. Potential overlapping toxicities for both agents include:

- Dermatologic disorders (pruritus, rash).
- GI disorders (diarrhea, mucosal inflammation, nausea, stomatitis, vomiting).
- Generalized disorders (anorexia, asthenia, decreased appetite, fatigue).
- Hematologic disorders (lymphoid, bone marrow depletion).
- Metabolic disorders (decreased blood chloride, hypercholesterolemia, hyperglycemia).

On the basis of current clinical experience and the previous list of potential overlapping toxicities, hyperglycemia, diarrhea, nausea, vomiting, fatigue, and rash are the most anticipated TEAEs associated with the MLN0128+MLN1117 combination regimen. These events are expected to be manageable.

During this study, risk mitigation strategies include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of TEAEs and serious adverse events (SAEs) by the sponsor.

The benefits of MLN0128 and MLN0128+MLN1117 are discussed in Section 4.1.2.

Further details are presented in the current editions of the MLN0128, MLN0128+MLN1117, and MLN1117 IBs.

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objectives of the study are:

- To compare the efficacy of single-agent MLN0128 versus single-agent everolimus in patients with mccRCC.
- To compare the efficacy of the combination of MLN0128+MLN1117 versus single-agent everolimus in patients with mccRCC.

5.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the safety and tolerability of MLN0128 and MLN0128+MLN1117.
- To compare the efficacy of the combination of MLN0128+MLN1117 versus single-agent MLN0128 in patients with mccRCC.
- To evaluate the efficacy (endpoints other than PFS; ie, overall survival [OS], time-to-progression [TTP], objective response rate [ORR], and clinical benefit rate [CBR]) among the 3 treatment groups.
- To collect plasma concentration-time data with sparse PK sampling to contribute to future population PK analysis.

5.3 Quality of Life Objective

The health-related quality of life (QOL) objective is:

- To assess the health-related QOL and symptoms as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS) questionnaire among the 3 treatment groups.

6.0 STUDY ENDPOINTS

6.1 Primary Endpoint

The primary endpoint is PFS.

6.2 Secondary Endpoints

The secondary endpoints are:

- The number and percentage of patients with TEAEs.
- OS.
- TTP.
- ORR (defined as complete response [CR]+partial response [PR] per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1).
- CBR (defined as CR+PR+stable disease [SD]) with SD of any duration, and CBR with SD duration of at least 4 months.

6.3 QOL Endpoints

The health-related QOL endpoints are:

- Changes from Baseline in functional and symptom scores, and global health status and QOL score from the EORTC QLQ-C30 and symptom scales from the FKSI-DRS questionnaire.

7.0 STUDY DESIGN

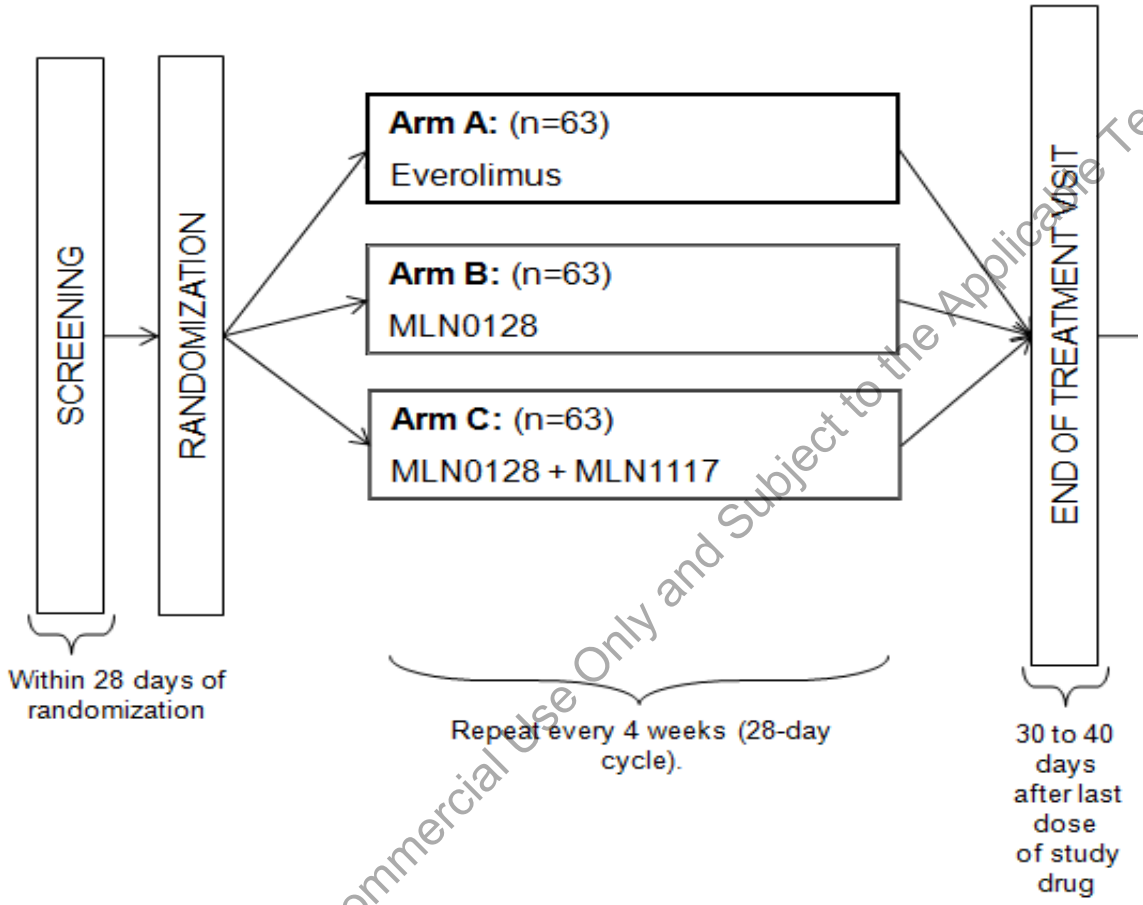
7.1 Overview of Study Design

This is a phase 2, open-label study of the safety and efficacy of MLN0128, as a single agent and in combination with MLN1117, in adult patients with advanced or mccRCC that has progressed on VEGF-targeted therapy. Eligibility will be determined during the Screening period, which may last for up to 28 days before the Cycle 1 Day 1 visit. Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study. Approximately 189 patients who meet the eligibility criteria will be stratified according to the number of prior lines of therapy (1, >1 prior line) and the International Metastatic Renal Cell Carcinoma Database Consortium risk category (favorable, intermediate, or poor) [22], and will be randomized at a ratio of 1:1:1 to one of 3 treatment arms:

- Arm A: single-agent everolimus.
- Arm B: single-agent MLN0128.
- Arm C: combination of MLN0128+MLN1117.

Patients will receive study drug(s) (ie, MLN0128, MLN1117, and everolimus) in 28-day cycles. Patients in Arm A will receive everolimus 10 mg QD according to current prescribing information in either the United States Prescribing Information (USPI) [23] or Summary of Product Characteristics (SmPC) [24] for everolimus. Patients in Arm B will receive MLN0128 30 mg orally once weekly (on Days 1, 8, 15, and 22 of a 28-day treatment cycle). Patients in Arm C will receive MLN0128 4 mg and MLN1117 200 mg orally both QD×3 days per week (on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle). Patients will receive MLN0128, MLN0128+MLN1117, or everolimus until they experience disease progression or unacceptable toxicity, withdraw consent, die, or transfer to the Post-Trial Access (PTA) program. The study design is displayed in Figure 7.a.

Figure 7.a Study Design



The rationale for the planned doses for Arm B and Arm C are described in Section 4.2.1.

Radiographic tumor evaluations will be performed by contrast-enhanced computed tomography (CT) scan with intravenous (IV) contrast or magnetic resonance imaging (MRI) with IV contrast, unless contraindicated. CT of the chest, and CT or MRI of the abdomen and pelvis, will be used to evaluate disease response according to RECIST version 1.1 [25]. Supplemental x-ray and/or bone scanning may be performed, but these methods are not suitable for lesion measurement. Radiographic tumor evaluations will be performed at the time points specified in Appendix A Schedule of Events.

Study data will be reviewed after the first 30 patients in each arm have received 2 cycles of study drug. If at the end of Cycle 2, 50% or more patients in a treatment arm (ie, Arm B [single agent MLN0128] or Arm C [MLN0128+MLN1117]) have either progressive disease or have died, or have discontinued study treatment due to treatment-related AEs, then that study arm may be closed. If both Arms B and C meet these criteria, then the study may be closed.

Throughout the study, toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective date 14 June 2010 [26]. Dose modification guidelines are in Section 9.3.

AEs will be assessed, and clinical laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of single-agent MLN0128 and MLN0128+MLN1117 in combination.

Sparse PK samples will be collected in Cycle 1 from all patients enrolled in Arms B and C for plasma PK analysis of MLN0128 (Arms B and C) and MLN1117 (Arm C). Blood samples for all PK analyses will be collected at the time points specified in the Treatment Arm B Sparse Pharmacokinetic Sample Breakdown and Treatment Arm C Sparse Pharmacokinetic Sample Breakdown.

Data generated in this study may be combined with data from other studies, in which the PK of MLN0128 or MLN1117 is characterized for a future population PK analysis.

7.2 Number of Patients

The study planned to enroll approximately 189 patients with mccRCC-from approximately 60 to 70 study centers in North America and Europe. A patient is considered to be enrolled in the study when he or she has been randomized into a treatment arm.

7.3 Duration of Study

Patients will receive study medication(s) until disease progression, unacceptable toxicity, withdrawal of consent, or study closure. Patients who discontinue study medication will complete an EOT visit 30 to 40 days after the last dose of study drug. The EOT visit should be conducted before the initiation of subsequent anticancer therapy, even if it occurs less than 30 days after the last dose of study drug.

A final analysis of PFS will be performed after the required number of events has been observed, which is expected approximately 9 months after the last patient has been randomized.

The study will be closed 2 years after the last patient is randomized or when the last patient discontinues study treatment.

8.0 STUDY POPULATION

8.1 Inclusion Criteria

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

1. Male or female patients aged 18 years or older.
2. Histologically confirmed RCC with a clear-cell component.
3. Evidence that the RCC is advanced or metastatic.
4. Radiologic evidence of progressive disease (according to RECIST version 1.1) either during or within 6 months after stopping their most recent systemic therapy for RCC before enrollment into this study.
5. At least 2 prior lines of systemic therapy for advanced metastatic ccRCC, including at least 1 prior line of VEGF-targeted therapy, but not more than 4 total prior lines of systemic therapy. Exposure to more than 1 line of VEGF-targeted therapy is acceptable. Patients may also have received prior therapies with interferon, IL-2, anti-PD1 antibodies, cabozantinib, or other experimental agents, but not prior therapy with any agent that targets PI3K, AKT, or mTOR.
6. Karnofsky performance status ≥70% (refer to Appendix D).
7. Life expectancy of ≥3 months.
8. 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 of contraception and 1 additional effective (barrier) method (See Appendix E), at the same time, from the time of signing the informed consent through 90 days (or longer, as mandated by local labeling [eg, USPI, SmPC, etc]) after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not 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 highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug (or longer, as mandated by local labeling [eg, USPI, SmPC, etc]), OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea

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

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

9. Suitable venous access for the study-required blood sampling.
10. Screening clinical laboratory values as specified below:
    - Absolute neutrophil count (ANC) ≥2000/μL and platelet count ≥100,000/μL.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of the normal range (ULN).
    - Total bilirubin ≤1.5×ULN.
    - Estimated creatinine clearance by Cockcroft-Gault ≥40 mL/min/1.73m^2 (see Appendix F).
    - Glycosylated hemoglobin (HbA1c) <7.0%, fasting serum glucose ≤130 mg/dL, and fasting triglycerides ≤300 mg/dL.
11. At least 14 days since the end of prior systemic VEGF-targeted treatment (ie, sunitinib, pazopanib, axitinib, or sorafenib), radiotherapy, or surgical procedure with resolution of all treatment-related toxicity (except alopecia and hypothyroidism) either to Grade 0 or 1 (NCI CTCAE version 4.03) or to Baseline.
12. At least 21 days since the last dose of bevacizumab, other antibody, or interferon.
13. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

8.2 Exclusion Criteria

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

1. Central nervous system (CNS) metastasis.
2. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active CNS disease, active infection, or any other condition that might compromise the patient's participation in the study.
3. Known human immunodeficiency virus infection.
4. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
5. Manifestations of malabsorption due to prior GI surgery, GI disease, or for an unknown reason that may alter the absorption of everolimus, MLN0128, or MLN1117. In addition, patients with enteric stomata are excluded.

6. Women who are either breast feeding or pregnant.
7. History of any of the following within the last 6 months before administration of the first dose of study drug:
    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures.
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures.
    - Requirement for inotropic support (excluding digoxin), or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
    - Placement of a pacemaker for control of rhythm.
    - New York Heart Association Class III or IV heart failure (see Appendix G).
    - Pulmonary embolism.
8. Significant active cardiovascular or pulmonary disease including:
    - Uncontrolled hypertension (ie, either systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg). Use of antihypertensive agents to control hypertension before Cycle 1 Day 1 is allowed.
    - Pulmonary hypertension.
    - Uncontrolled asthma or oxygen saturation <90% by arterial blood gas analysis or pulse oximetry on room air.
    - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention; or history of valve replacement.
    - Medically significant (symptomatic) bradycardia.
    - History of arrhythmia requiring an implantable cardiac defibrillator.
    - Baseline prolongation of the rate-corrected QT interval (QTc; eg, repeated demonstration of QTc interval >480 msec, or history of congenital, long-QT syndrome, or torsades de pointes).
9. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer, superficial bladder cancer, very low risk prostate on observation, or carcinoma in situ of any type are not excluded if they have undergone complete resection.
10. Prior therapy with agents that target PI3K, AKT, or mTOR. Patients with known hypersensitivity to everolimus or rapamycin derivatives are also excluded.

11. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
12. Patients who have taken a PPI within 3 days before receiving the first dose of study drug.

9.0 STUDY DRUG

9.1 Study Drug Administration

All protocol-specific criteria for administration of MLN0128 or MLN1117 must be met and documented before study drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

For Arm B, weekly MLN0128 will be administered with a light meal. Examples of a light meal are provided in Table 9.a. Patients should begin consuming the light meal no more than 30 minutes before taking the weekly dose of MLN0128. It is recommended that each dose of MLN0128 be given orally with approximately (at least) 8 ounces (240 mL) of water.

Table 9.a Examples of a Light Meal

	Low-Fat Breakfast	Light Snack
Nutritional information	Approximately 330 calories, with 9 g of fat	Approximately 100 to 300 calories, with 1.5 g of fat
Example	2 slices of toast with 1 teaspoon of low-fat margarine, 1 teaspoon of jelly, and 8 oz of skimmed milk	3.63 oz pudding cup or 1 slice of toast with 1 teaspoon of jelly and 8 oz of skimmed milk

For Arm C, MLN0128 and MLN1117 will be administered on an empty stomach. Patients should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose. Each dose of MLN0128 and MLN1117 will be given orally with approximately (at least) 8 ounces (240 mL) of water.

Cycles consist of 28 days for all treatment arms. In Treatment Arm A, everolimus will be administered QD (every day of a 28-day treatment cycle). In Treatment Arm B, MLN0128 will be administered once weekly (on Days 1, 8, 15, and 22 of a 28-day treatment cycle) and should be taken on the same day of each week. In Treatment Arm C, MLN0128 and MLN1117 will be administered together, 3 consecutive days per week (on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle), and should be taken on the same days of each week.

Patients should be instructed to take their study medication at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. MLN0128 and MLN1117 should always be taken together, at the same time, when dosed on the same day. Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. If a patient does not take their MLN0128 and/or MLN1117 doses within 12 hours after the scheduled dosing time (for patients in Arm A or C) or within 24 hours after the scheduled dosing time (for patients in Arm B), then the dose should be skipped and considered a missed dose. Patients should record any missed doses in their diary (see the Study Manual) and resume drug administration at the next scheduled time with the prescribed dosage.

If severe emesis or mucositis prevents the patient from taking scheduled doses, that dose will be skipped. If emesis occurs after study medication ingestion, the dose will not be readministered, and

patients should resume dosing at the next scheduled time with the prescribed dosage. Patients should record the occurrence of the emesis in their dosing diaries (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses.

9.2 Reference/Control Therapy

Everolimus can be taken either with or without food according to either the USPI [23] or SmPC [24]. Patients should be instructed to take their study medication at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time.

9.3 Dose Modification Guidelines

This section describes dose modification guidelines for study drugs MLN0128 and MLN1117. Any dose modifications for everolimus should follow the guidelines provided in the current USPI [23] or SmPC [24] for everolimus. Refer to Section 9.7 for dose adjustment guidelines related to the management of clinical events.

9.3.1 Intrapatient Dose Escalation

Intrapatient dose escalation is not allowed.

9.3.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

MLN0128 and MLN1117 should be administered in continuous cycles, which should continue unless the patient has a Grade 3 or greater MLN0128- and/or MLN1117-related event. Guidelines for dose interruption are in Section 9.3.3 and for dose reduction are in Section 9.3.4.

9.3.3 Criteria for Dose Interruption During a Cycle

Administration of MLN0128 and the combination of MLN0128+MLN1117 should be withheld for treatment-related toxicities that are Grade 3 or higher despite supportive treatment per standard clinical practice.

The following nonhematologic toxicities attributed to either MLN0128 or MLN1117 would not require dose interruption:

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

9.3.4 Criteria for Dose Reduction

9.3.4.1 Single-Agent MLN0128 Once Weekly (Arm B)

MLN0128 administration should be withheld for treatment-related AEs that are Grade 3 or higher despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 (or Grade 2 for hyperglycemia or rash, as detailed in Sections 9.7.1 and 9.7.4, respectively) or to baseline values within 3 weeks of interrupting treatment, then the patient may resume study treatment at a dose reduced by 1 level (Table 9.b). If a patient does not tolerate 10 mg, then the investigator and the project clinician should discuss whether the patient would benefit from a further dose reduction.

Table 9.b Dose Modifications for Single-Agent MLN0128

Dose Level	Dose Regimen	MLN0128 Capsules: Number and Strength
0	30 mg QW	Six 5-mg capsules
–1	20 mg QW	Four 5-mg capsules
–2	15 mg QW	Three 5-mg capsule
–3	10 mg QW	Two 5-mg capsules

9.3.4.2 MLN0128+MLN1117 (Arm C)

The primary principle for dose reduction in Arm C is to maintain the 200 mg dose of MLN1117, which is considered the minimum efficacious dose when combined with MLN0128. Thus, the dose of MLN0128 will be reduced, if necessary, while the dose and schedule of MLN1117 is maintained when study drug administration is resumed (Table 9.c).

If the Grade 3 or higher event that led to dose interruption resolves to Grade 1 (or Grade 2 for hyperglycemia or rash, as detailed in Sections 9.7.1 and 9.7.4, respectively) or baseline value within 3 weeks of interrupting treatment, then the patient may resume combination study treatment provided that treatment with study drug is thought to be beneficial for the patient by the investigator and with the sponsor's approval. In this case, the patient may resume study treatment with MLN1117 at 200 mg QD×3 days and MLN0128 reduced by 1 dose level; for interruptions due to Grade 3 elevations of ALT or AST, study treatment may be resumed at the prior dose without dose reduction (Section 9.7.8).

Table 9.c Dose Modifications for MLN0128 in Combination with MLN1117

	Dose QD×3 days per week		
Dose Level	**MLN0128**	**MLN1117**	**MLN0128 Capsules: Number and Strength**
0	4 mg	200 mg	One 3 mg capsule and one 1 mg capsule
–1	3 mg	200 mg	One 3 mg capsule
–2	2 mg	200 mg	Two 1 mg capsules
–3	1 mg	200 mg	One 1 mg capsule

9.3.5 Criteria for Discontinuation of Study Drug

For patients in Arm A, everolimus should be discontinued according to the current guidance provided in either the USPI [23] or SmPC [24] for everolimus.

If study drug administration (in Arm B or Arm C) is delayed for more than 3 weeks (21 consecutive days) due to study drug-related toxicity despite supportive treatment per standard clinical practice, or more than 3 dose reductions of study drug are required in a patient, then study drug treatment should be stopped. However, if the patient has evidence of clinical benefit and is considered to possibly benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review and approval by the project clinician, or participate in the PTA program if available.

For all patients, the EOT visit should be completed within 30 to 40 days after the last dose of study drug.

9.4 Excluded Concomitant Medications and Procedures

9.4.1 Excluded Concomitant Medications and Procedures for Arm A

The current USPI [23] and SmPC [24] for everolimus list the excluded medications for patients receiving everolimus in Arm A of the study.

In addition, these specific exclusions also apply to Arm A:

- Other investigational agents including mTOR, PI3K, and AKT inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery (patients can have palliative radiation or surgery during the study for pre-existing lesions). Palliative therapy for target lesions is not allowed.
- Systemic corticosteroids (either IV or oral steroids), unless necessary for treatment of a study drug-related AE (eg, rash). Inhalers and low-dose replacement therapy are allowed.

9.4.2 Excluded Concomitant Medications and Procedures for Arms B and C

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient as of the first administration of study drug through 30 days following the last dose will be recorded on the designated electronic case report form (eCRF).

The following medications, therapies, and procedures are prohibited during the study:

- Other investigational agents including mTOR, PI3K, and AKT inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery (patients can have palliative radiation or surgery during the study for pre-existing lesions).
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of a study drug-related AE (eg, rash).
- Strong cytochrome P450 (CYP) 1A2 inhibitors and CYP inducers should be administered only with caution and at the discretion of the investigator (see Appendix H for a list of these agents). Alternative treatments, if available, should be considered.
- Concomitant administration of any PPI is prohibited only for patients randomized to MLN0128 + MLN1117. Patients receiving PPI therapy before enrollment must stop using the PPI 3 days before their first dose of study drugs. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
- Histamine H2 receptor antagonists may be allowed, if needed, provided that the histamine H2 receptor antagonist is not taken within 12 hours before and within 6 hours after MLN0128 or MLN0128+MLN1117 administration. Patients receiving histamine H2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H2 receptor antagonists include ranitidine, famotidine, and nizatidine. Cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first-choice H2 receptor antagonist (see Appendix H).
- Administration of neutralizing antacids and calcium preparations is permitted except from 4 hours before until 2 hours after MLN0128 or MLN0128+MLN1117 administration. Some antigas preparations may also have antacid properties, and should also not be permitted from 4 hours before until 2 hours after study drug administration.

9.4.3 Potential for Drug-Drug Interactions with MLN0128 and/or MLN1117

On the basis of in vitro drug metabolism studies, MLN1117 is primarily metabolized by CYP3A4 (72%), with minor contributions from CYPs 1A2 (12%), 2C9 (9%), and 2C8 (6%). Recently completed in vitro metabolism experiments in human hepatocytes using 14C-labeled MLN0128 suggest that MLN0128 is metabolized primarily via CYP1A2 (approximately 31%-40%), with a minor contribution from CYP3A4 (approximately 11%-22%). These data suggest that MLN0128 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified nonuridine diphosphate glucuronosyltransferase pathway (approximately 18%). The new data differ from the

previous in vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in MLN0128 metabolism. Neither MLN1117 nor MLN0128 inhibits or induces any of the major CYP enzymes. On the basis of this information, the risk of a drug-drug interaction between MLN1117 and MLN0128 is considered to be low. In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with MLN0128 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator during the study (see Appendix H).

There is potential for MLN1117 to affect the PK of breast cancer resistance protein (BCRP) substrates (eg, methotrexate, imatinib, topotecan, lapatinib, rosuvastatin, etc) and organic cation transporter protein 1 (OCT1) or organic cation transporter protein 2 (OCT2) substrates (eg, metformin, cimetidine, amantadine, famotidine, pindolol, etc; see Appendix I). If patients require treatment with medications that are known substrates of these transporters, then these agents should be administered with caution or alternative treatment options should be considered. It is recommended that patients requiring metformin for treatment of hyperglycemia resulting from MLN0128+MLN1117 administration that treatment should begin with the lowest effective dose of metformin, and patients should have their blood or serum glucose monitored closely.

9.5 Permitted Concomitant Medications and Procedures

Prophylactic use of antiemetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose and subsequent doses of study drug, as needed throughout the study, and as clinically indicated per standard practice.

Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

9.6 Precautions and Restrictions

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with study drug. Examples of live vaccines are intranasal influenza, measles, mumps, rubella, oral polio, Bacille Calmette-Guerin, yellow fever, varicella, and TY21a typhoid vaccines.

No dietary restrictions will be imposed on study patients other than fasting for glucose monitoring (refer to Sections 9.7.1, 10.4.13, and 10.4.14). Patients receiving MLN0128 and MLN1117 in Arm C should refrain from eating or drinking for 2 hours before and 1 hour after each dose (per Section 9.1).

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

Patients should be encouraged to drink at least 20 ounces of fluids a day, especially on days requiring fasting (per protocol), with administration of IV fluids in the clinic as indicated to avoid dehydration.

It is not known what effects either MLN0128 or MLN1117 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods and after study treatment as specified below.

Female patients must meet one 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 of contraception and 1 additional effective (barrier) method (See Appendix E), at the same time, from the time of signing of the informed consent through 90 days (or longer, as mandated by local labeling [eg, USPI, SmPC, etc]) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug (or longer, as mandated by local labeling [eg, USPI, SmPC, etc]), OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate sperm during the course of this study or within 120 days after receiving their last dose of study drug.

9.7 Management of Clinical Events

For current guidance on the management of clinical events for patients receiving everolimus in Arm A, refer to either the USPI [23] or SmPC [24] for everolimus.

For patients being treated with single-agent MLN0128 QW (Arm B), MLN0128 administration should be withheld for treatment-related AEs that are Grade 3 or higher despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 (or Grade 2 for

hyperglycemia or rash, as detailed in Sections 9.7.1 and 9.7.4, respectively) or to baseline values within 3 weeks of interrupting treatment, then the patient may resume study treatment at a dose reduced by 1 level (Table 9.b).

For patients being treated with MLN0128+MLN1117 (Arm C), the primary principle for dose reduction is to maintain the 200 mg dose of MLN1117, which is considered the minimum efficacious dose when combined with MLN0128. Thus, the dose of MLN0128 will be reduced, if necessary, while the dose and schedule of MLN1117 is maintained when study drug administration is resumed (Table 9.c).

If the Grade 3 or higher event that led to dose interruption resolves to Grade 1 (or Grade 2 for hyperglycemia or rash, as detailed in Sections 9.7.1 and 9.7.4, respectively) or baseline value within 3 weeks of interrupting treatment, then the patient may resume combination study treatment with MLN1117 at 200 mg QD×3 days and MLN0128 reduced by 1 dose level.

9.7.1 Management of Hyperglycemia

On the basis of the clinical experience in MLN0128 trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with MLN0128 and have been either Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since the institution of a standard regimen for early treatment of hyperglycemia.

All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff. The investigator may choose to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting glucose >ULN ≤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. The investigator should consult an endocrinologist, if needed, to aid in optimizing the patient's hyperglycemia treatment plan.

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

If any fasting serum glucose reading performed at the site indicates hyperglycemia (>ULN or ≥110 mg/dL), the study staff should first confirm that the patient was fasting at the time of blood specimen collection (ie, nothing by mouth for at least 8 hours before collection). To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines (Table 9.d) are provided to aid the investigator in initiating antiglycemic therapies.

Table 9.d Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
1	Fasting blood sugar >ULN to 160 mg/dL	• Continue close monitoring of blood sugar. • Initiate oral hypoglycemic agent.	None
2	>160 to 250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥3	>250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin.	Hold study drug(s) until ≤Grade 2. (a) 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 the dose of MLN0128 by 1 dose level (See Section 9.3.4). (b) • >2 weeks: stop study drug(s).

Prevention/Prophylaxis:

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

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.
(b) As described in Section 9.3.4 and Section 9.7, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

9.7.2 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided in Table 9.e.

Table 9.e Management of Hyperlipidemia

Grade	Description	Treatment	Dose Modification
1	Cholesterol: >ULN-300 mg/dL Triglycerides: >150-300 mg/dL	None	None
2	Cholesterol: >300-400 mg/dL Triglycerides: >300-500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥500 mg/dL should be treated urgently, due to risk of pancreatitis.	Maintain dose, if tolerable. If toxicity becomes intolerable, interrupt study drug(s) until recovery to ≤Grade 1. Re-initiate study drug(s) at the same dose level. (a)
3	Cholesterol: >400-500 mg/dL Triglycerides: >500-1000 mg/dL	Same as for Grade 2.	Hold study drug(s) until recovery to ≤Grade 1, then reinitiate study drug(s) with the dose of MLN0128 reduced by 1 level (Section 9.3.4). (a) (b)
4	Cholesterol: >500 mg/dL Triglycerides: >1000 mg/dL	Same as for Grade 2.	Same as for Grade 3.

Prevention/Prophylaxis:

- Recommend lifestyle modifications, as appropriate (balanced diet, limit alcohol consumption, increase physical activity).

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.
(b) As described in Section 9.3.4 and Section 9.7, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

9.7.3 Management of Oral Mucositis

Guidance on study drug dose modification for patients with oral mucositis is provided in Table 9.f.

Table 9.f Management of Oral Mucositis

Grade	Description	Treatment	Dose Modification
1	Asymptomatic or mild symptoms.	• Nonalcoholic mouth wash, or 0.9% salt water rinse. • Consider topical corticosteroids at earliest signs of mucositis.	None
2	Moderate pain, not interfering with oral intake. Modified diet indicated.	• Topical analgesic mouth treatments. • Topical corticosteroids. • Initiate antiviral or antifungal therapy, if indicated.	• Maintain study drug(s) dose if tolerable. (a) • Hold study drug(s) if intolerable until recovery to ≤Grade 1, then restart at same dose.
3	Severe pain, interfering with oral intake.	• Same as for Grade 2. • Consider intralesional corticosteroids.	• Hold study drug(s) until recovery to ≤Grade 1, then restart study drug(s) with the dose of MLN0128 reduced by 1 level (Section 9.3.4). (a) (b)
4	Life-threatening consequences.	• Same as for Grade 2 • Consider intralesional corticosteroids	• Stop study drug(s). (a)

Prevention/Prophylaxis:

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

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.
(b) As described in Section 9.3.4 and Section 9.7, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

9.7.4 Management of Rash

Patients who develop Grade 4 rash should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity. Grade 4 rash is defined as rash acneiform/papulopustular with papules and/or pustules covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences (NCI CTCAE version 4.03, effective date 14 June 2010 [26]).

Guidance on study drug dose modification for patients with rash is provided in Table 9.g.

Table 9.g Management of Rash

Grade	Description	Treatment	Dose Modification
≤2	Macules/papules covering ≤30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment and/or oral antihistamines or antibiotics.	None
3	Macules/papules covering >30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment, oral antihistamines, oral antibiotics, and/or pulsed steroids.	Hold study drug(s) until ≤Grade 2. (a) Resume study drug(s) based on timing of recovery: • ≤3 weeks: reduce the dose of MLN0128 by 1 dose level (Section 9.3.4). (a) (b) • >3 weeks: stop study drug(s). (a)

Patients who develop Grade 4 rash should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity. Grade 4 rash is defined as rash acneiform/papulopustular with papules and/or pustules covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection, with IV antibiotics indicated; life threatening consequences.

Prevention/Prophylaxis:

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

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.
(b) As described in Section 9.3.4 and Section 9.7, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

9.7.5 Management of Nausea/Vomiting

Guidance for patients with nausea and/or vomiting is provided in Table 9.h.

Table 9.h Management of Nausea/Vomiting

Grade	Description	Treatment	Dose Modification
≤2	Loss of appetite with or without decreased oral intake; 1 to 5 episodes of vomiting within 24 hours.	• Maximize antiemetic therapy. • Consider IV fluid hydration.	None
≥3	Inadequate oral intake; ≥6 episodes of vomiting within 24 hours.	• Maximize antiemetic therapy. • Initiate tube feeding, IV fluids, or TPN.	If experienced for ≤72 hours, hold MLN0128 until ≤Grade 1, then resume MLN0128 without dose modification. If experienced for >72 hours despite optimal therapy, hold study drug(s) until ≤Grade 1, then resume treatment with the dose of MLN0128 reduced by 1 level. (a) (b)

Prevention/Prophylaxis:

Prophylactic use of antiemetic, antinausea, and antidiarrheal medications are encouraged and may be used before each MLN0128+MLN1117 dosing as needed throughout the study.

IVF=intravenous fluids, TPN=total parental nutrition.
(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.
(b) As described in Section 9.3.4 and Section 9.7, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

9.7.6 Management of Cardiac Abnormalities

Management of Patients With Possible Cardiac Instability

For patients showing signs of cardiac instability after MLN0128+MLN1117 administration, additional monitoring onsite before clinic discharge should be considered.

Management of Patients With Left Ventricular Dysfunction

Guidance for MLN0128+MLN1117 dose adjustment for patients with left ventricular dysfunction is provided in Table 9.i.

Table 9.i Management of Left Ventricular Dysfunction

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

LLN=lower limit of normal, LVEF=left ventricular ejection fraction.
(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.

Management of Patients with QTc Interval Prolongation

Patients who experience persistent symptomatic Grade 3 or Grade 4 QTc prolongation without another cause should permanently discontinue study treatment.

Guidance for MLN0128+MLN1117 dose adjustment for patients exhibiting a prolonged QTc interval is provided in Table 9.j.

Table 9.j Management of QTc Interval Prolongation

Grade	Description	Treatment	Dose Modification
2	480 msec <QTc <501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication, etc).	None; continue study drug(s) at the same dose and schedule. (a)
≥3	QTc ≥501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication).(a) Consider a formal consult by a cardiologist; Notify the sponsor's project clinician; Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.	Hold study drug(s). (b) Patients who experience persistent symptomatic Grade 3 or Grade 4 QTc prolongation without another cause should permanently discontinue study treatment.

(a) A list of medications known to prolong the QTc interval can be found at https://www.crediblemeds.org/new-drug-list/
(b) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.

9.7.7 Management of Other Nonhematologic Toxicities

Guidance on dose adjustment for patients with other nonhematologic toxicities is provided in Table 9.k.

Patients who develop Grade 4 nonhematological toxicities (with the exception of isolated non-clinically significant laboratory values) should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity.

Table 9.k Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Initiate appropriate medical therapy and monitor.	If tolerable, then no adjustment is required.
2	Moderate; minimal, local or noninvasive intervention indicated.	Initiate appropriate medical therapy and monitor.	• If tolerable, no adjustment required. • If toxicity becomes intolerable, hold study drug(s) until recovery to ≤Grade 1, then reinitiate at same dose.
≥3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated		Hold study drug(s) until recovery to ≤ Grade 1. Reinitiate study drug(s) with the dose of MLN0128 reduced by 1 level (Section 9.3.4) (a) (b) Patients who develop Grade 4 nonhematological toxicities (with the exception of isolated non-clinically significant laboratory values) should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤ Grade 1 severity.

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.
(b) As described in Section 9.3.4 and Section 9.7, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

9.7.8 Management of AST/ALT Elevations

Patients who develop Grade 3 or Grade 4 AST/ALT elevation in combination with Grade 2 total bilirubin elevation when alternative causes cannot be identified (ie, Hy's Law) should permanently discontinue study treatment.

Guidance on dose adjustment for patients with AST/ALT elevations is provided in Table 9.l.

Table 9.l Management of AST/ALT Elevations

Grade	Description	Treatment	Dose Modification
1	>ULN to 3×ULN	None	None
2	Asymptomatic with levels 3 to 5×ULN; >3×ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.	• Closely monitor LFTs at least weekly or more frequently as indicated. • Assess patient for other causes of transaminitis (eg, past medical history, concomitant medications).	None
3	>5 to 20×ULN; >5×ULN for >2 weeks	Same as for Grade 2.	Hold study drug(s) until ≤Grade 1; Restart MLN0128 and MLN1117 at the same doses. (a) Permanently discontinue study treatment if in combination with Grade 2 total bilirubin elevation when alternative causes cannot be identified.
4	>20×ULN	Same as for Grade 2.	Stop study drug(s). (a)
Prevention/Prophylaxis: Ensure proper screening of patients for study participation.			

LFTs=liver function tests.
(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.

9.7.9 Management of Noninfectious Pneumonitis

Guidance for the management of pneumonitis is provided in Table 9.m.

Table 9.m Management of Noninfectious Pneumonitis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic: Radiographic findings only.	Rule out infection and closely monitor.	None
2	Symptomatic: Not interfering with activities of daily living.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Interrupt study drug(s) • When symptoms ≤Grade 1, reinitiate study drug(s) with the dose of MLN0128 reduced by 1 level (Section 9.3.4). • If no recovery within 4 weeks, then discontinue study drug(s). (a,b)
3	Symptomatic: Interfering with activities of daily living; Requires administration of oxygen.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Interrupt study drug(s) until symptoms resolve to ≤Grade 1. (a) • Consider reinitiating study drug(s) with the dose of MLN0128 reduced by 1 level (Section 9.3.4). (b) • If toxicity recurs at Grade 3, discontinue study drug(s).
4	Life-threatening: Ventilatory support indicated.	Rule out infection and consider treatment with corticosteroids.	Stop study drug(s). (a)

(a) Study drug(s) refers to MLN0128 and MLN1117. If a patient is taking both MLN0128 and MLN1117, then both agents should be held.
(b) As described in Section 9.3.4 and Section 9.7, dose reduction applies only to MLN0128 treatment. The dose of MLN1117 should be maintained at 200 mg when resuming treatment after an interruption of study drug or dose modification of MLN0128.

9.7.10 Management of Opportunistic Infections

Opportunistic infections, such as *Pneumocystis jirovecii* (*carinii*) pneumonia (PJP, PCP), are a known risk for patients receiving everolimus treatment; and prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive agents is required (refer to Section 9.4 and Section 9.5 for guidance regarding concomitant medication use). Although opportunistic infections, including PCP, have not been observed in patients receiving MLN0128 or MLN1117 treatment, opportunistic infections should be considered during diagnostic evaluation of symptomatic patients.

9.7.11 Blinding and Unblinding

Not applicable. This is an open-label study.

9.8 Description of Investigational Agents

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

All 3 dose strengths are formulated into size-2 capsules, and each dose strength is differentiated by color, as listed below:

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

MLN1117 will be supplied as 100 mg capsules for oral administration. Each 100 mg capsule contains 100 mg of MLN1117 and the following inactive ingredients: hard gelatin capsule and small amount of colloidal silicon dioxide. See the MLN0128, MLN1117, and MLN0128+MLN1117 IBs for full details.

Everolimus is commercially available and will be supplied by Millennium as 10 mg, 5 mg, and 2.5 mg tablets for oral administration.

9.9 Preparation, Reconstitution, and Dispensation

MLN0128 and MLN1117 dosage forms will be provided in labeled bottles in accordance with all applicable regulations. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN0128 and MLN1117 are anticancer drugs and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 and MLN1117 capsules.

9.10 Packaging and Labeling

MLN0128 and MLN1117 will be provided by Millennium and will be handled at the investigative site as open-label material.

MLN0128 will be provided in 30-ct, 60-cc high-density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal. MLN1117 will be provided in 14-ct, 30-cc HDPE bottles with child-resistant caps and induction seal.

MLN0128 and MLN1117 are packaged and labeled in accordance with all applicable regulations.

Everolimus will be supplied by Millennium to all participating sites. Everolimus will be provided as blister packs and will be labeled per all requirements specified by governing regulations.

9.11 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN0128 and MLN1117 should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F to 86°F). All temperature excursions will be reported 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 MLN0128 and MLN1117 supplies should be used before the retest expiry date.

Everolimus should be stored according to instructions provided in the USPI [23] or SmPC [24].

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, 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 MLN0128 and MLN1117 are an investigational agents, they should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), the skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will receive instructions for home storage and administration of MLN0128 and 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.

Please refer to the Study Manual for additional instructions.

9.12 Other Protocol-Specified Materials

Not applicable.

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 Millennium project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country (where applicable), the Interactive Web Response System provider, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

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 institutional review board (IRB)/independent ethics committee (IEC).

10.3 Treatment Group Assignments

A centralized randomization procedure IXRS will be used for treatment group assignment. Patients who meet the eligibility criteria will be stratified according to the number of prior lines of therapy (1, >1 prior line) and the International Metastatic Renal Cell Carcinoma Database Consortium risk category (favorable, intermediate, or poor) [22], and will be randomized at a ratio of 1:1:1 to one of 3 treatment arms:

- Arm A: single-agent everolimus, 10 mg QD (every day of a 28-day treatment cycle).
- Arm B: single-agent MLN0128, 30 mg QW (on Days 1, 8, 15, and 22 of a 28-day treatment cycle).
- Arm C: combination of MLN0128 4 mg+MLN1117 200 mg, both QD×3 days per week (on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle).

The first dose of study drug must be administered within 5 days after randomization on study.

10.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, and EOT. Evaluations during the Screening period are to be conducted within 28 days before administration of the first dose of study drug. Unless otherwise noted, evaluations during the Treatment period must occur before study drug administration. Tests and procedures should be performed on schedule for all visits but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons, starting after the completion of Cycle 2 Day 1. The

timing of PK assessments is specified in the Treatment Arm B Sparse Pharmacokinetic Sample Breakdown and Treatment Arm C Sparse Pharmacokinetic Sample Breakdown.

All EOT evaluations should occur within 30 (+10) days after the last dose of study drug, or before the start of subsequent antineoplastic therapy.

Refer to the Schedule of Events for the 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 Patient Demographics

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

10.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 10.4.8.

10.4.4 Physical Examination

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

10.4.5 Patient Height and Weight

Height will be measured only during Screening (within 28 days before the first dose of study drug [ie, MLN0128, MLN0128+MLN1117, or everolimus]). Body weight will be measured at the visits specified in the Schedule of Events.

10.4.6 Vital Signs

Vital sign measurements include diastolic and systolic blood pressure, heart rate, and temperature. Vital signs will be measured at the visits specified in the Schedule of Events.

10.4.7 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 Day 1 of every cycle with negative results available before the first dose may be administered in that cycle. A serum pregnancy test may also be performed within 3 days before dosing in place of the Day 1 urine test.

10.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the first dose of study drug through 30 days after the last dose of study drug. See Section 9.4 and Section 9.5 for a list of medications and therapies that are prohibited and/or allowed during the study.

10.4.9 AEs

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

10.4.10 Enrollment

A patient is considered to be enrolled in the study when they have been randomized into a treatment arm. Procedures for completion of the enrollment information are described in the Study Manual.

10.4.11 ECG

A single, 12-lead ECG will be administered at the time points specified in the Schedule of Events. Additional ECGs may be obtained as clinically indicated.

10.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Clinical laboratory evaluations will be performed as outlined below:

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedule of Events. Specimens for analysis of the clinical chemistry, hematologic, and coagulation parameters shown in Table 10.a and urine specimens for analysis of the parameters shown in Table 10.b will be obtained as specified in Schedule of Events.

Table 10.a Clinical Chemistry, Hematology, and Coagulation Tests

Hematology and Coagulation	Serum Chemistry	
Hematocrit	Albumin	Gamma glutamyl transferase
Hemoglobin	Alkaline phosphatase	Glucose
Leukocytes with differential	ALT	HbA1c (only at the timepoints specified in the Schedule of Events).
Neutrophils (ANC)	Amylase	Lactate dehydrogenase
Platelet (count)	AST	Magnesium
Activated partial thromboplastin time	Bilirubin (total and direct)	Phosphate
Prothrombin time/international normalized ratio	Blood urea nitrogen or urea	Potassium
	Calcium (total)	Sodium
	Carbon dioxide or bicarbonate	Protein (total)
	Chloride	Urate
	Creatinine	

Table 10.b Clinical Urinalysis Tests

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

Prospective monitoring for hyperlipidemia will be managed through fasting lipid testing. Sampling for the fasting lipid profile (Appendix A (Schedule of Events).

Table 10.c) will be obtained at the times specified in Appendix A (Schedule of Events).

Table 10.c Fasting Lipid Profile

Fasting Lipid Profile	
Cholesterol (total)	High-density lipoprotein cholesterol
Triglycerides	Low-density lipoprotein cholesterol

10.4.13 Fasting Serum Glucose

Fasting serum glucose will be measured in the clinic at the time points specified in Appendix A (Schedule of Events). Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. For patients receiving everolimus in Arm A or MLN0128 and MLN1117 in Arm C, the sample should be taken approximately 2 hours after dose administration with patients

continuing to fast until after that sample is taken. For patients receiving MLN0128 QW in Arm B, the sample should be taken predose; after predose blood draws are complete, patients receiving MLN0128 QW in Arm B should consume a light meal before dosing (Section 9.1). In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.

10.4.14 In-Home Daily Fasting Glucose Monitoring

In addition to obtaining fasting glucose levels at the clinic visits as outlined in Appendix A (Schedule of Events), all patients randomized to receive MLN0128 (ie, Arms B and C) will be given a glucometer to monitor their daily fasting blood glucose (FBG) levels at home. The level should be collected daily, predose on dosing days, and at approximately the same time each day. Before checking their blood glucose levels, patients should fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment). After fasted testing is complete, patients in Arm B should consume a light meal before MLN0128 dosing (Section 9.1).

On Cycle 1 Day 1, the patient will be provided an in-home glucometer. Patients will be trained on proper use of the glucometer and instructed to collect a daily FBG level every morning (predose on dosing days), starting on Cycle 1 Day 2. 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. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.

The patient will be instructed to contact the site immediately if the value is abnormal (ie, ≥150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic.

If no irregularities in the FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgement and approval. Patients will continue to notify the investigator of FBG levels that exceed 150 mg/dL and, if blood glucose levels are not well controlled, or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. See also Section 9.7.1.

10.4.15 Disease Assessment

Patients will undergo contrast-enhanced imaging (CT or MRI) to monitor the overall disease burden unless contraindicated for a particular patient in accordance with RECIST version 1.1 [25]. As much as possible, the same imaging modalities and methods should be used for patients throughout the study. CT scans of the chest, in addition to CTs or MRIs of the abdomen and pelvis, will be obtained at Screening and all subsequent time points. Supplemental x-ray and/or bone scanning may be performed, but these methods are not suitable for lesion measurement. Objective assessments will be performed at each time point as described in the Schedule of Events. Anatomical measurements (summed across target lesions) and the presence of nontarget lesions

will be documented at Baseline/Screening, and the status of target, nontarget, and new lesions will be assessed at each subsequent imaging time point. When possible, the same qualified physician will interpret results to reduce variability.

Disease assessment images will be collected and reviewed by a sponsor-specified central imaging vendor. Radiographic images will also be maintained at the site, and test results and physician's findings will be filed in patient source documents.

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

10.4.16 PK Measurements

Sparse PK sampling to characterize the PK of MLN0128 (Arms B and C) and MLN1117 (Arm C), including patients who receive crossover treatment, will be performed at the times indicated in the Treatment Arm B Sparse Pharmacokinetic Sample Breakdown and Treatment Arm C Sparse Pharmacokinetic Sample Breakdown.

When the timing of a PK blood sample coincides with vital sign measurements, the vital sign measurement should be obtained before the PK blood sample.

In addition to the PK sample collections specified, a blood sample to measure MLN0128 and MLN1117 concentrations should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged by the investigator to be treatment-related, irrespective of the cycle, day, or stage of occurrence of the AE. The date and exact time of the unscheduled sample collection should be recorded. Details on the collection, storage, processing, handling, and shipping of PK samples are in the Study Manual.

PK data for MLN0128 and MLN1117 collected in this study may be combined with similar data from other studies for future population PK analysis. The results of the population PK analysis will not be presented in the clinical study report and may be presented in a separate population PK analysis report at a later time.

10.4.17 Pharmacodynamic Measurements

No pharmacodynamic measurements will be made.

10.4.18 DNA Measurements

CCI

[redacted]

CCI [redacted]

10.4.19 Banked Tumor Specimen Measurements; Tumor Biopsies

Banked formalin-fixed, paraffin-embedded tumor tissue (or fresh tumor biopsy as described below in this section) should be obtained at Screening for assessment of candidate biomarkers predictive of response, including, but not limited to somatic gene alterations and expression of markers such as PTEN, PIK3CA, mTOR, and phosphorylated (p-) AKT, p-S6, and p-4E-BP1. It is anticipated that developing these potential biomarkers of antitumor activity mediated by the combination of MLN0128 and MLN1117 will require analysis of the data from this study in combination with data from other clinical studies of this combination and each single agent.

If either a paraffin-embedded tumor block or a minimum of 15 unstained slides are not available, then the patient will be required to undergo a fresh tumor biopsy at Screening as indicated in the Schedule of Events. If fresh tumor biopsy collection is unsuccessful, enrollment is contingent upon discussion with the sponsor.

Detailed instructions for the collection, processing, and shipment of the fresh tumor biopsy samples are provided in the Study Manual.

10.4.20 QOL and Symptom Assessments

The QOL instruments, EORTC QLQ-C30 and FKSI-DRS, will be administered as specified in Appendix A (Schedule of Events), and they must be completed before other assessments are performed or study drug is administered.

The EORTC QLQ-C30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning); 1 global health status scale; 3 symptom scales (fatigue, nausea and vomiting, and pain); and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) (See Appendix J). The time recall period for this instrument is 1 week (the past week). The EORTC QLQ-C30 is a reliable and valid measure of health-related QOL in patients with cancer [27]. The instrument consists of a brief (30-item) questionnaire that has been validated and used in many countries.

The FKSI-DRS is a validated, 9-item questionnaire derived from the 15-item FSKI-15 questionnaire designed to assess the effect of disease-related symptoms on patients with kidney cancer [28] (see Appendix K).

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.

The maximum duration of treatment for patients will be 24 months unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued treatment beyond 24 months.

10.6 Completion of Study

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

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

- AE.
- Protocol violation.
- Progressive disease.
- Symptomatic deterioration.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

Patients must discontinue study drug if they experience disease progression or unacceptable toxicity, or if they become pregnant.

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

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.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database. Data on survival may be obtained from publicly available databases and sources.

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 Post-Trial Access Program

If an open-label, rollover, PTA program becomes an option and the investigator and the sponsor agree that a patient would derive benefit from continued treatment or might be harmed without continued access to the medication, the patient may be given the opportunity to enroll.

In the event of study closure by the sponsor, continued access to study treatment will be terminated for patients who are no longer benefiting from treatment (eg, their disease has progressed or treatment is no longer tolerable), the benefit-risk assessment is no longer favorable, or an appropriate alternative therapy becomes available. The PTA program may be terminated in a country or geographic region or terminated by the sponsor if study treatment can no longer be supplied or study drug becomes available either commercially or via another access mechanism.

Related SAEs during the PTA program must be reported to Takeda Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur after the EOT visit. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of SAEs.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 PTE Definition

A PTE 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 AE 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 SAE 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 one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home,

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

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE version 4.03, effective date 14 June 2010 [26]. 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/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

11.2 Procedures for Recording and Reporting AEs and SAEs

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 PTEs (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 PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

CCI

United States and Canada

CCI

Planned hospital admissions or surgical procedures for an illness or disease that existed 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 PTEs, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE version 4.03, effective date 14 June 2010 [29]. 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 AEs 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 PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the informed consent form 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 or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

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 or during the PTA program, 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 (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 or during the PTA program, 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 contact the Medical Information [redacted] and report the complaint. The contact information is as follows:

Medical Information Center: [redacted]
Phone:
Fax:
Email:
Hours: Mon-Fri, 9 AM-7 PM, ET

Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

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 [redacted] (refer to Section 11.2).

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

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

12.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

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 randomized subject.

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, 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,

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

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

14.1.1 Analysis Sets

- Full analysis set: all randomized patients.
- Safety analysis set: patients who receive at least 1 dose of study drug.
- Response-evaluable analysis set: patients who receive at least 1 dose of study drug, have measurable disease at Baseline, and have 1 postbaseline disease assessment.

14.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic (age, sex) and baseline characteristics (weight, height, and other parameters, as appropriate) will be summarized by treatment arm (ie, everolimus, MLN0128, or MLN0128+MLN1117).

14.1.3 Efficacy Analysis

Primary Efficacy Endpoint

The primary endpoint is PFS, defined as the time from the date of randomization to the date of first documentation of progression or death due to any cause, whichever occurs first. For a patient whose disease has not progressed and is last known to be alive, PFS will be censored at the last response assessment that is SD or better. The primary efficacy analysis will be based on the full analysis set.

The Kaplan-Meier method will be used to analyze the distribution of PFS for each treatment arm. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% CIs, hazard ratio along with associated 95% CI, and Kaplan-Meier estimates at relevant time points will be presented. The primary hypothesis is to be tested at the 0.15 significance level (2-sided). The p-values from a stratified log-rank test and hazard ratios and will be presented for each pair-wise comparison.

Secondary Efficacy Endpoints

Secondary efficacy endpoints include OS, ORR, TTP, CBR with SD of any duration, and CBR with SD duration of at least 4 months.

OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed using similar methods as the primary endpoint of PFS in the full analysis set.

Objective response rate is defined as the proportion of patients who achieve a best response of CR or PR. CBR is defined as the proportion of patients who achieve a best response of CR, PR, or SD. The CBR will also be presented for a best response of CR, PR, and SD of at least 4 months. A stratified Cochran-Mantel-Haenszel test will be used to compare ORR and CBR between treatment arms. The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each pair-wise comparison.

TTP is defined as the time from the date of randomization to the date of first documentation of progression. For a patient whose disease has not progressed, TTP will be censored at the last response assessment that is SD or better. TTP will be analyzed using similar methods as the primary endpoint of PFS in the full analysis set.

14.1.4 PK Analysis

Sparse PK data for MLN0128 and MLN1117 are being collected to contribute to a future population PK analysis. These data may be combined with data from other studies in which the PK of MLN0128 or MLN1117 is characterized for population PK analysis. The results of population PK analysis will be presented in a separate report.

14.1.5 Pharmacodynamic Analysis

Not applicable.

14.1.6 Other Analyses

Patient-Reported Outcomes

Patient-reported outcome (PRO) assessments using the EORTC QLQ-C30 and FKSI-DRS questionnaires will be analyzed to determine if response to therapy and side effects of therapy are accompanied by measurable changes in the PROs. Published scoring manuals and guidelines will be used to generate scale scores and handle missing data.

Descriptive statistics for baseline values, actual values, and the change from Baseline will be presented at each scheduled time point for each of the functional and symptom scores, and the global health status/QOL score from the EORTC QLQ-C30, and the FKSI-DRS score. Differences between treatment arms in the EORTC QLQ-C30 and FKSI-DRS scores will be evaluated. Longitudinal analysis of PRO scores will be performed using linear mixed models.

14.1.7 Safety Analysis

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 analysis set. Exposure to each study drug (ie, MLN0128, MLN1117, and everolimus) will be summarized and reasons for discontinuation will be tabulated. Safety will be summarized by treatment arm (everolimus, MLN0128, MLN0128+MLN1117).

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.
- SAEs.

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

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

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from Baseline to the worst postbaseline value.

Concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term in the safety analysis set.

ECG Analysis

ECG intervals (QT and QTc with Fridericia correction, and PR), QRS duration, and ventricular rate will be summarized at each scheduled time point, along with mean change from Baseline to each post-treatment time point. The number and percentage of patients with ECG abnormalities will be summarized at each time point.

14.2 Interim Analysis and Criteria for Early Termination

Study data will be reviewed after the first 30 patients in each arm have received 2 cycles of study drug. If at the end of cycle 2, 50% or more patients in a treatment arm (ie, Arm B [single agent MLN0128] or Arm C (MLN0128+MLN1117) have either progressive disease or have died, or have discontinued study treatment due to treatment-related AEs, then that study arm may be closed. If both Arms B and C meet this criteria, then the study may be closed.

14.3 Determination of Sample Size

Approximately 189 patients will be enrolled in the 3 treatment arms.

The primary efficacy endpoint is PFS. Assuming that the median PFS is 5 months for everolimus [20] and that MLN0128 (either as a single agent or in combination with MLN1117) can improve

the median PFS to 8 months (hazard ratio of 0.625), then a total of 95 PFS events are needed for each pair-wise comparison and approximately 63 patients are required for each treatment arm. The calculations are based on a power of 80%, 2-sided alpha of 15%, and a dropout rate of 10% due to either lost to follow-up or withdrawal of consent.

The sample size for the study assumes the total accrual will be approximately 14 months, where 10% of the patients are enrolled within the first 3 months and 40% are enrolled at the end of 7 months. The final analysis for the pair-wise comparisons of PFS between single-agent MLN0128 and everolimus and between the combination of MLN0128+MLN1117 and everolimus will occur approximately 9 months after the last patient is randomized.

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 IEC, 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.

The investigator should document all protocol deviations.

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.

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 IB, 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.

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 before 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 before 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 before the 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.

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.

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 (as applicable), 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. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International Variations and Trends in Renal Cell Carcinoma Incidence and Mortality. Eur Urol 2015;67(3):519-30.
2. Li P, Znaor A, Holcatova I, Fabianova E, Mates D, Wozniak MB, et al. Regional Geographic Variations in Kidney Cancer Incidence Rates in European Countries. European Urology 2014.
3. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nature Reviews Urology 2010;7(5):245-57.
4. Lipworth L, Tarone RE, Lund L, McLaughlin JK. Epidemiologic characteristics and risk factors for renal cell cancer. Clin Epidemiol 2009;1:33-43.
5. Gudas LJ, Fu L, Minton DR, Mongan NP, Nanus DM. The role of HIF1alpha in renal cell carcinoma tumorigenesis. J Mol Med (Berl) 2014;92(8):825-36.
6. Brugarolas J. Molecular genetics of clear-cell renal cell carcinoma. Journal of Clinical Oncology 2014;32(18):1968-76.
7. Audenet F, Yates DR, Cancel-Tassin G, Cussenot O, Roupret M. Genetic pathways involved in carcinogenesis of clear cell renal cell carcinoma: genomics towards personalized medicine. BJU Int 2012;109(12):1864-70.
8. Pantuck AJ, Zeng G, Belldegrun AS, Figlin RA. Pathobiology, prognosis, and targeted therapy for renal cell carcinoma: exploiting the hypoxia-induced pathway. Clin Cancer Res 2003;9(13):4641-52.
9. Laplante M, Sabatini, DM. mTOR Signaling in Growth Control and Disease. Cell 2012;149(2):274-93.
10. Laplante M, Sabatini DM. mTOR Signaling. Cold Spring Harb Perspect Biol 2012;4(2).
11. Sabatini DM. mTOR and cancer: insights into a complex relationship. Nature Reviews Cancer 2006;6(9):729-34.
12. Benjamin D, Colombi M, Moroni C, Hall MN. Rapamycin passes the torch: a new generation of mTOR inhibitors. Nature Reviews Drug Discovery 2011;10(11):868-80.
13. Vilar E, Perez-Garcia J, Tabernero J. Pushing the envelope in the mTOR pathway: the second generation of inhibitors. Molecular Cancer Therapeutics 2011;10(3):395-403.
14. Thoreen CC, Kang SA, Chang JW, Liu Q, Zhang J, Gao Y, et al. An ATP-competitive mammalian target of rapamycin inhibitor reveals rapamycin-resistant functions of mTORC1. Journal of Biological Chemistry 2009;284(12):8023-32.
15. Thoreen CC, Sabatini DM. Rapamycin inhibits mTORC1, but not completely. Autophagy 2009;5(5):725-6.
16. Chresta CM, Davies BR, Hickson I, Harding T, Cosulich S, Critchlow SE, et al. AZD8055 is a potent, selective, and orally bioavailable ATP-competitive mammalian target of rapamycin

kinase inhibitor with in vitro and in vivo antitumor activity. Cancer Research 2010;70(1):288-98.

17. Rodrik-Outmezguine VS, Chandarlapaty S, Pagano NC, Poulikakos PI, Scaltriti M, Moskatel E, et al. mTOR kinase inhibition causes feedback-dependent biphasic regulation of AKT signaling. Cancer Discov 2011;1(3):248-59.
18. O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, Smith D, et al. mTOR Inhibition Induces Upstream Receptor Tyrosine Kinase Signaling and Activates Akt. Cancer Res 2006;66(3):1500-8.
19. Tabernero J, Rojo F, Calvo E, Burris H, Judson I, Hazell K, et al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 2008;26(10):1603-10.
20. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer 2010;116(18):4256-65.
21. Cho DC, Cohen MB, Panka DJ, Collins M, Ghebremichael M, Atkins MB, et al. The efficacy of the novel dual PI3-kinase/mTOR inhibitor NVP-BEZ235 compared with rapamycin in renal cell carcinoma. Clinical Cancer Research 2010;16(14):3628-38.
22. Ko JJ, Xie W, Kroeger N, Lee JL, Rini BI, Knox JJ, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. Lancet Oncol 2015;16(3):293-300.
23. AFINITOR (everolimus) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2015.
24. Afinitor [Summary of Product Characteristics]. Horsham, West Sussex, UK: Novartis Europharm Limited, 2014.
25. 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.
26. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.
27. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993;85(5):365-76.

28. Cella D, Yount S, Brucker PS, Du H, Bukowski R, Vogelzang N, et al. Development and validation of a scale to measure disease-related symptoms of kidney cancer. Value in Health 2007;10(4):285-93.

29. 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.

30. Karnofsky D, Burchenal J. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod C, editor. Evaluation of Chemotherapeutic Agents: Symposium Held at the New York Academy of Medicine. New York: Columbia University Press; 1949, p. 191-205.

31. Peus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak 2013;13:72.

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

33. The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed. Boston, MA: Little, Brown & Co; 1994.

Appendix A Schedule of Events

Schedule of Events

	Screening (a)	Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6 and Beyond		EOT(b)
	Days -28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	Day 28	Day 1	Day 1	Day 1	Day 28	
Informed consent	X											
Inclusion/exclusion criteria	X											X
Demographics	X											
Medical history	X											
Physical examination (c)	X	X	X	X	X	X			X			X
Height	X											
Weight	X	X		X		X		X	X	X		X
Vital signs (d)	X	X	X	X	X	X		X	X	X		X
Karnofsky performance status	X	X		X		X		X	X	X		X
Single, 12-lead ECG (e)	X	X		X		X		X	X	X		X
EORTC-QLQ-C30		X		X		X		X	X	X		X
FKSI-DRS		X		X		X		X	X	X		X
Radiographic tumor assessment by RECIST version 1.1 (f)	X						X				X	
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through 30 days after the last dose of study drug										
AE reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug										
	SAEs (g) will be reported from signing of the informed consent form through 30 days after the last dose of study drug.											
Dosing (h)												
Treatment Arm A		Everolimus QD continuously										
Treatment Arm B		MLN0128 QW continuously										
Treatment Arm C		MLN0128+MLN1117 QD×3 each week continuously (on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle)										
Patient diary review (i)		X	X	X	X	X	X	X	X	X	X	X
Samples/Laboratory Assessments												
Pregnancy test (j)	X1	X1		X1			X1	X1		X1		
Hematology/Chemistry (k)	X1	X1	X1	X1	X1		X1	X1		X1		X1
Coagulation (PT/INR, aPTT)	X1	X1		X1			X1	X1		X1		X1
Fasting serum glucose (l)	X1	X1		X1			X1	X1		X1		X1
In-home daily fasting glucose monitoring (m)		X										

Schedule of Events

	Screening (a)	Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6 and Beyond		EOT(b)
	Days -28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	Day 28	Day 1	Day 1	Day 1	Day 28	
HbA1c	X					X1				Q 3 cycles (n)		
Fasting lipid profile (o)	X			X		X		X	X	X		X
Urinalysis	X	X	X	X		X		X				X
CCI [redacted]												
Tumor tissue (banked) or fresh biopsy sample (q)	X											
Blood sample for PK (r)		Refer to Treatment Arm B Sparse Pharmacokinetic Sample Breakdown and Treatment Arm C Sparse Pharmacokinetic Sample Breakdown										

aPTT=activated partial thromboplastin time, C=cycle, INR=international normalized ratio, OSFU=overall survival follow-up, PC EOT=Precrossover End-of-Treatment, PFSFU=progression-free survival follow-up, PT=prothrombin time, Q=every.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons, starting after the completion of Cycle 2 Day 1.

(a) Unless otherwise noted, the Screening visit (and all screening assessments) must occur within 28 days before the day of the first dose of study drug (Cycle 1 Day 1). The informed consent form may be signed more than 28 days before Cycle 1 Day 1. Screening assessments performed no more than 3 days before D1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

(b) Patients will attend an EOT/Early Termination visit 30 to 40 days after receiving their last dose of study drug or at the start of subsequent anticancer therapy. If subsequent anticancer therapy is required before 30 days after the last dose, the EOT/Early Termination visit should be conducted before the initiation of subsequent anticancer therapy. The study will be closed when the last patient discontinues treatment.

(c) Complete physical examination at Screening. Symptom-directed physical examinations at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Day 1 on each cycle thereafter and during the EOT/Early Termination visit. The Cycle 1 Day 1 physical examination and medical history are not required if the physical examination at Screening was conducted and medical history obtained within 4 days before administration of the first dose of study drug (Cycle 1 Day 1).

(d) Perform vital signs measurement before study drug administration except on Cycle 1 Day 15, when patients should take their dose or doses of study drug early in the morning at home. Vital sign measurements include blood pressure (diastolic and systolic), heart rate, and temperature.

(e) Single, 12-lead ECGs will be collected predose on Day 1 of every cycle and during the EOT visit. When the timing of an ECG coincides with blood samples, the ECG should be completed first. All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in a supine position.

(f) Radiological evaluations will be employed to assess the status of the patient's underlying disease. Contrast-enhanced imaging of the same imaging modality (CT or MRI) should be used for a patient throughout the study unless contraindicated. Baseline CT of the chest and CT or MRI scan of the abdomen and pelvis must be obtained within 4 weeks before the first dose of study drug. Contrast-enhanced CT or MRI scans will be obtained on Day 28 (±3 days) of every 3 cycles (ie, Cycle 3 Day 28, Cycle 6 Day 28, etc). A contrast-enhanced

CT or MRI scan is not required at the EOT visit for patients with documented radiographic disease progression.
After the patient has completed 12 cycles of treatment, disease assessment may be performed every 6 cycles (after previous assessment) or otherwise per investigator's discretion.

(g) Including serious PTEs; see Section 11.0.

(h) The first dose of study drug must be administered within 5 days after randomization on study. In Arm B, weekly MLN0128 will be administered with a light meal; in Arm C, MLN0128+MLN1117 will be administered on an empty stomach (see Section 9.1).

(i) The study center staff will check the patient diary versus the patient's supply of study drug (ie, MLN0128, MLN1117, or everolimus, as applicable) to assess compliance.

(j) A serum pregnancy test will be performed for women of childbearing potential at Screening. A urine pregnancy test must be performed predose on Day 1 of every cycle with negative results available before the first dose may be administered in that cycle. A serum pregnancy test may also be performed within 3 days before dosing in place of the Day 1 urine test.

(k) Refer to Section 10.4.12 for a list of the required clinical laboratory assessments. Laboratory assessments may be performed within 1 day before the required study visit. Safety laboratory results must be available and reviewed by the investigator before study drug administration. Electrolyte levels should be corrected as needed before study drug administration.

(l) Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. For patients receiving everolimus in Arm A or MLN0128 and MLN1117 in Arm C, the sample should be taken approximately 2 hours after dose administration with the patient continuing to fast until after that sample is taken. For patients receiving MLN0128 QW in Arm B, the sample should be taken predose; after predose blood draws are complete, patients receiving MLN0128 QW in Arm B should consume a light meal before dosing (Section 9.1). In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.
See Sections 9.7.1 and 10.4.14 for further instructions.

(m) Patients will be given a glucometer on Cycle 1 Day 1 to monitor daily fasting glucose levels at home and will be instructed to notify the study clinician when the fasting glucose is abnormal (ie, ≥150 mg/dL). See Sections 9.7.1 and 10.4.14 for further instructions.

(n) Every 3 cycles from Cycle 6 (ie, Cycle 6, Cycle 9, etc).

(o) Total cholesterol, high density lipoprotein cholesterol, low density lipoprotein, and triglycerides.

(p) CCI [redacted]

(q) Archived tumor tissue, either paraffin blocks or a minimum of 15 unstained slides (paraffin blocks preferred) should be obtained from a previous resection or biopsy that was done as part of the patient's standard care. These samples will be evaluated for candidate biomarkers predictive of response. Tumor tissue is to be collected only from enrolled patients and can be collected and sent to the sponsor after initiation of protocol treatment. If archival tumor tissue is not available, a tumor biopsy can be performed before the patient begins treatment with study drug(s). See Section 10.4.19 for requirements.

(r) Blood specimens for PK analysis will be collected from patients randomized to Arms B (single-agent MLN0128) and C (MLN0128+MLN1117 combination) perr the Treatment Arm B Sparse Pharmacokinetic Sample Breakdown and Treatment Arm C Sparse Pharmacokinetic Sample Breakdown. Blood specimens for PK analysis will not be collected from patients randomized to Arm A (single-agent everolimus).

Treatment Arm B Sparse Pharmacokinetic Sample Breakdown

	Cycle 1	
	Day 1 (a)	Day 15 (b)
	PK	PK
At time of clinic visit (anytime postdose)		X1
Approximately 1 hour after previous PK sample collection		X1
1-2 hours postdose (±15 min)	X1	
3-6 hours postdose (±30 min)	X2 (c)	

This PK sampling schedule applies to patients receiving crossover treatment as well as to patients initially randomized to Arm B.
X#=the number of samples required (eg, 2 samples=X2).
(a) Subjects should bring a light meal with them to this visit. After completion of fasting serum glucose sampling, subjects will begin consuming the meal within 30 min before dosing, after which they will take their regularly scheduled doses of MLN0128. The exact date/time of meal consumption, MLN0128 dosing, and PK sampling must be recorded in the eCRF. Over the course of the study, a distribution of sampling times within this time range is encouraged.
(b) Subjects will take their regularly scheduled doses of MLN0128 at home with a light meal and will record the exact date/time of meal consumption and dose administration in their subject diaries. Subjects will then report to the clinic for the scheduled visit, during which they will provide PK samples. The date/time of meal consumption, dosing, and PK sampling must be recorded in the eCRF. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged.
(c) Two samples will be taken no less than 1 hr apart within the specified window.

Treatment Arm C Sparse Pharmacokinetic Sample Breakdown

	Cycle 1	
	Day 1	Day 15
	PK	PK
At time of clinic visit (anytime postdose) (a)		X1
Approximately 1 hour after the last PK sample		X1
1-2 hours postdose (b)	X1	
3-6 hours postdose (b)	X1	

This PK sampling schedule applies to patients receiving crossover treatment as well as to patients initially randomized to Arm C.
X#=the number of samples required (eg, 2 samples=X2).
(a) On Cycle 1 Day 15, patients should take their dose or doses of study drug early in the morning at home, and note the date and time that the dose was taken. Patients should also note the date/time of the previous dose. Two postdose PK plasma specimens will be collected at the clinic. The first specimen may be collected after arrival at the clinic and the second specimen collected approximately 1 hour after the first. The date/time of dosing and PK sampling must be recorded in the eCRF. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged.
(b) On Cycle 1 Day 1, PK plasma specimens can be collected at any time during the sampling window. The date and time of MLN0128 dosing on Cycle 1 Day 1 and the date/time of PK sampling must be recorded in the eCRF. Over the course of the study, a distribution of sampling times within the windows is encouraged.

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 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 (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before 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 Code of Federal Regulations (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.

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.
13. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other personally identifiable information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Karnofsky Performance Status

Karnofsky Performance Status

Condition	Percent	Description
Able to carry on normal activity and to work. No special care is needed.	100	Normal, no complaints, no evidence of disease.
	90	Able to carry on normal activity, minor signs or symptoms of disease.
	80	Normal activity with effort, some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled, requires special care and assistance.
	30	Severely disabled, hospitalization is indicated although death not imminent.
	20	Hospitalization necessary, very sick, active supportive treatment necessary.
	10	Moribund, fatal processes progressing rapidly.
	0	Dead.

Sources:

Karnofsky, DA, Burchenal, JH. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In Evaluation of Chemotherapeutic Agents: Symposium Held at the New York Academy of Medicine, MacLeod CM (ed). (New York, Columbia University Press), 1949, 191-205. [30]

Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak. 2013 Jul 19;13:72. [31]

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 (b).
- Intrauterine hormone-releasing system (b).
- Bilateral tubal occlusion (b).
- Vasectomized 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 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.

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

(c) Vasectomized 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 vasectomized 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 Cockcroft-Gault Equation

For men:

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

OR

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

For women:

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

OR

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41 [32].

Appendix G New York Heart Association Classification of Cardiac Disease

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256 [33].

Appendix H List of Relevant Cytochrome P450 Inhibitors and Inducers

Moderate CYP1A2 Inhibitors		
Cimetidine	Methoxsalen	
Strong CYP1A2 Inhibitors		
Fluvoxamine	Ciprofloxacin	
Clinically Significant Enzyme Inducers		
Carbamazepine	Rifabutin	St. John's wort
Phenobarbital	Rifampin	Phenytoin
Rifapentine		

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.
Note that these lists are not exhaustive.

Appendix I List of BCRP, OCT1, and OCT2 Substrates

BCRP, OCT1, and OCT2 Substrates

BCRP Substrates	OCT1 and OCT2 Substrates
Methotrexate	Metformin
Imatinib	Cimetidine
Topotecan	Amantadine
Lapatinib	Famotidine
Rosuvastatin	Pindolol

Appendix J EORTC QLQ-C30 Version 3

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): |_|_|_|_|_|_|_|_|

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix K Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms

FKSI -DRS

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
BRM 3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
RCC2	I have had blood in my urine	0	1	2	3	4

Appendix L Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 10 are indicated. The corresponding text has been revised throughout the protocol.

Change #1: Removed long-term follow-up and the option for cross-over treatment, and added the option for patients to transfer to a Post-Trial Access program.

The primary change occurs in Section 7.1 Overview of Study Design.

Initial wording:	Patients will receive MLN0128, MLN0128+MLN1117, or everolimus until they experience disease progression or unacceptable toxicity, withdraw consent, or die. Patients who experience progressive disease per RECIST version 1.1 during treatment with everolimus may be eligible to cross over to receive treatment with either MLN0128 or MLN0128+MLN1117. Patients who discontinue study treatment for reasons other than progressive disease will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the End-of-Treatment (EOT) visit, then every 3 months (±1 week) until disease progression or start of another anticancer therapy, whichever occurs first. After disease progression or start of another anticancer therapy, patients will be followed for OS every 3 months (±1 week).
Amended or new wording:	Patients will receive MLN0128, MLN0128+MLN1117, or everolimus until they experience disease progression or unacceptable toxicity, withdraw consent, **die, or transfer to the Post-Trial Access program**. ~~or die. Patients who experience progressive disease per RECIST version 1.1 during treatment with everolimus may be eligible to cross over to receive treatment with either MLN0128 or MLN0128+MLN1117. Patients who discontinue study treatment for reasons other than progressive disease will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the End-of-Treatment (EOT) visit, then every 3 months (±1 week) until disease progression or start of another anticancer therapy, whichever occurs first. After disease progression or start of another anticancer therapy, patients will be followed for OS every 3 months (±1 week).~~

The study design figure (Figure 7.a) was also modified.

This change also occurs in Section 2.0, Section 7.3, Section 10.4, Section 10.9, and the Schedule of Events.

Rationale for Change: The study is to be closed.

Change #2: Study closure was defined as then the last patient discontinues treatment.	
The primary change occurs in Section 7.3 Duration of Study.	
Initial wording:	The study will be closed 2 years after the last patient is randomized or when the last patient discontinues study treatment.
Amended or new wording:	The study will be closed ~~2 years after the last patient is randomized or~~ when the last patient discontinues study treatment**.**
This change also occurs in Section 2.0 Study Summary and the Schedule of Events.	
Rationale for Change: The study is be closed.	
Change #3: A new section was added (10.10) detailing the Post-Trial Access program.	
New or amended wording:	**If an open-label, rollover, PTA program becomes an option and the investigator and the sponsor agree that a patient would derive benefit from continued treatment or might be harmed without continued access to the medication, the patient may be given the opportunity to enroll.** **In the event of study closure by the sponsor, continued access to study treatment will be terminated for patients who are no longer benefiting from treatment (eg, their disease has progressed or treatment is no longer tolerable), the benefit-risk assessment is no longer favorable, or an appropriate alternative therapy becomes available. The PTA program may be terminated in a country or geographic region or terminated by the sponsor if study treatment can no longer be supplied or study drug becomes available either commercially or via another access mechanism..** **Related SAEs during the PTA program must be reported to Takeda Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur after the EOT visit. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of SAEs.**
Rationale for Change: A PTA program was added to allow continued treatment after study closure for any patients receiving benefit.	

Change #4: Modified the exclusion criterion relating to PPIs.
The primary change occurs in Section 8.2 Exclusion Criteria #5,
Initial wording: 12. Patients requiring daily or chronic use of a proton pump inhibitor (PPI) and/or having taken a PPI within 7 days before receiving the first dose of study drug.
Amended or new wording: 12. Patients who have taken a PPI within ~~7~~ 3 days before receiving the first dose of study drug.
Rationale for Change: This change was made to allow more flexibility in patient enrollment based on data on MLN0128 metabolism.
This change also occurs in Section 2.0.
Change #5: Revised the restrictions on concomitant use of PPIs.
The primary change occurs in Section 9.4.2 Excluded Concomitant Medications and Procedures for Arms B and C.
Initial wording: • Concomitant administration of any PPI is not permitted during the study. Patients receiving PPI therapy before enrollment must stop using the PPI 7 days before their first dose of study drugs. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
Amended or New Wording: • Concomitant administration of any PPI is ~~not permitted during the study~~ **prohibited only for patients randomized to MLN0128 + MLN1117**. Patients receiving PPI therapy before enrollment must stop using the PPI ~~7~~ **3** days before their first dose of study drugs. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
Rationale for Change: This change was made to update the recommendations on concomitant medication use during the study based on data on MLN0128 metabolism.

Change #6: Physical examinations after Screening were changed to symptom-directed physical examinations.

The primary change occurs in the Schedule of Events.

Initial wording:	Complete physical examination at Screening, at Cycle 1 Day, Cycle 1 Day 15, Cycle 2 Day 1, Cyclle 2 Day 15, Day 1 of each cycle therafter and during the EOT/Early Termination Visit.
Amended or new wording:	Complete physical examination at Screening**. Symptom-directed physical examinations** at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Day 1 on each cycle thereafter, and during the EOT/Early Termination visit.

Rationale for Change: Complete physical examinations were not felt necessary at subsequent visits.

Change #7: The requirement for a confirmatory scan 4 weeks from the previous can for patients with a CR or PR was removed.

The primary change occurs in the Schedule of Events.

Deleted text:	~~A confirmatory scan should be performed at approximately 4 weeks from the previous scan for all patients with a complete or partial response.~~

Rationale for Change: The confirmatory scan was not felt necessary.

Change #8: A recommendation was added for radiographic assessments every 6 months, or at the investigator's discretion, after 12 cycles of treatment.

The primary change occurs in the Schedule of Events.

New wording:	**After the patient has completed 12 cycles of treatment, disease assessment may be performed every 6 cycles (after previous assessment) or otherwise per investigator's discretion.**

Rationale for Change: To clarify timing of assessments after 12 cycles of treatment.

Change #9: The requirement for weight to be measured at Day 15 of Cycles 1 and 2 was removed.

The primary change occurs in the Schedule of Events.

Rationale for Change: Weight measurement was not felt necessary at these timepoints.

Amendment 10 (France) to A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of Single-Agent MLN0128 and the Combination of MLN0128+MLN1117 Compared With Everolimus in the Treatment of Adult Patients With Advanced or Metastatic Clear-Cell Renal Cell Carcinoma That Has Progressed on Vascular Endothelial Growth Factor-Targeted Therapy

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	06-Dec-2018 19:16 UTC
	Clinical Pharmacology Approval	06-Dec-2018 20:10 UTC
	Clinical Science Approval	06-Dec-2018 20:59 UTC
	Clinical Science Approval	06-Dec-2018 21:23 UTC