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

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C31005

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

PHASE 2

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Prepared by:

CCI [redacted]

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1.1 APPROVAL SIGNATURES

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CBR	clinical benefit rate
CR	complete response
CT	computed tomography
CCI	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End-of-Treatment (visit)
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
HbA1c	glycosylated hemoglobin, hemoglobin A1c
HR	hazard ratio
IV	intravenous; intravenously
IRT	interactive response technology
mccRCC	metastatic clear-cell renal cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MLN0128	also known as TAK-228
MLN1117	also known as TAK-117
MRI	magnetic resonance imaging
mTOR	mechanistic (or mammalian) target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PIK3CA	phosphoinositide-3-kinase, catalytic alpha polypeptide
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
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

SAE	serious adverse event
SD	stable disease
TAK-117	MLN01117
TAK-228	MLN0128
TEAE	treatment-emergent adverse event
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

4.0 OBJECTIVES

4.1 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.

4.2 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.

4.3 Quality of Life Objectives

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

- To assess the HRQL and symptoms as measured by the EORTC-QLQ-C30 questionnaire and the FACT-Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS) questionnaire among the 3 treatment groups.

4.4 Exploratory Objectives

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4.5 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), 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) or Summary of Product Characteristics (SmPC) 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 QDx3 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, 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).

Radiographic tumor evaluations (CT scan with intravenous [IV] contrast or MRI as clinically indicated) of the chest, abdomen, and pelvis will be used to evaluate disease response according to RECIST Version 1.1.

Throughout the study, toxicity will be evaluated according to NCI CTCAE Version 4.03, effective date 14 June 2010.

Adverse events 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). 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.

Main analysis will be conducted when the required number of PFS events has been reached and then the final analysis when all patients have discontinued the study.

There will be one interim analysis. 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.

Potential for crossover treatment

Patients in the single-agent everolimus arm (Arm A) who have radiographically confirmed disease progression may be allowed to receive crossover treatment with single-agent MLN0128 or the combination of MLN0128+MLN1117. Once documented disease progression has been confirmed, patients referred for crossover will complete the Precrossover EOT visit as soon as possible. Patients must meet all applicable study eligibility criteria at the time of crossover (eg, the limit of a total of 4 lines of prior systemic therapy would not apply if on-study everolimus was their fifth line of treatment), and eligibility for crossover will be confirmed by the sponsor's project clinician (or designee). Eligible patients will then be randomized via the interactive voice and/or web response system (IXRS) in a 1:1 ratio to either single-agent MLN0128 or MLN0128+MLN1117.

Crossover treatment must begin after a 7-day washout period and within 28 days of documented disease progression. The first dose of single-agent MLN0128 or MLN0128+MLN1117 will be Cycle 1 Day 1 of the crossover treatment. Patients may receive crossover treatment until they experience disease progression on crossover treatment, unacceptable toxicity, they withdraw consent, or they are no longer considered by the investigator to be deriving clinical benefit from the crossover treatment.

Only the data collected during the study treatment in the initial single-agent everolimus arm will be included in the planned efficacy and safety analyses for the study. After crossover treatment begins, safety and efficacy data will be collected and presented separately.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is Progression Free Survival (PFS).

5.2 Secondary Endpoints

The secondary endpoints are:

- The number and percentage of patients with treatment-emergent adverse events.
- Overall survival (OS).
- Time-to-progression (TTP).
- Objective response rate (ORR; defined as complete response [CR]+partial response [PR] per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1).
- Clinical benefit rate (CBR; defined as CR+PR+stable disease) with SD of any duration
- CBR with SD duration of at least 4 months

5.3 Quality of Life Endpoints

The HRQL endpoints are:

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

5.4 Exploratory Endpoints

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6.0 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 [1] 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4.

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, 25th and 75th percentiles (where specified), minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data. For summaries of categorical variables percentages are based on the number of subjects with non-missing values unless otherwise specified (e.g. objective response rate, clinical benefit rate).

Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, the normal approximation methods will be employed unless otherwise specified.

All statistical tests and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values should be presented to 3 decimal places, with values less than 0.001 presented as <0.001. Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate. Percentages will be presented to 1 decimal place.

A month is operationally defined to be 30.4375 days.

Where specified, there will be two pair-wise comparisons between everolimus vs. MLN0128 and between everolimus vs. MLN0128 + MLN1117.

7.1.1 Methods for Handling Missing Data

For efficacy and safety data, no imputation of values for missing data will be performed. For patient reported outcomes, handling of missing data is discussed in section 7.10. Data imputation rules for incomplete dates are described in Appendix B.

7.1.2 Definitions of Baseline Values

In general, for efficacy endpoints the last observed measurement prior to randomization will be considered the baseline measurement. For safety endpoints, the last observation before first dose of study drug will be considered the baseline measurement. For patient-reported outcomes the last observed measurement on or before the date of first dose of study drug will be considered the baseline measurement.

7.1.3 Definition of Study Days

For the purposes of efficacy data summary, Day 1 is defined as the date of randomization. For visits (or events) that occur on or after randomization, Day is defined as (date of visit [event] –

date of randomization + 1). For visits (or events) that occur prior to randomization, Day is defined as (date of visit [event] – date of randomization). There is no Day 0.

For the purposse of safety data summary or calculations of time since baseline, Study Day 1 is defined as the date on which a subject is administered their first dose of study drug. For visits (or events) that occur on or after the first dose of study drug, study day is defined as (date of visit [event] – date of first dose of study drug + 1). For visits (or events) that occur prior to Study Day 1, study day is defined as (date of visit [event] – date of first dose of study drug). There is no Study Day 0.

7.2 Analysis Sets

- Full analysis set: all randomized patients. Patients will be analyzed according to the randomization assignment. The full analysis set will be used for the primary efficacy analysis of PFS, and secondary efficacy endpoints including OS and TTP.
- Safety analysis set: patients who receive at least 1 dose of study drug. Patients will be analyzed according to the treatment arm actually received. The safety analysis set will be used for all safety analyses. In addition, the safety analysis set will be used for a sensitivity analysis of secondary efficacy endpoints ORR, CBR, CBR-16 and the best overall response and patients will be analyzed according to the randomization assignment.
- Response-evaluable analysis set: patients who receive at least 1 dose of study drug, have measurable disease at Baseline, and have 1 post-Baseline disease assessment. Patients will be analyzed according to the randomization assignment. The response-evaluable analysis set will be used for the secondary efficacy endpoints of ORR, CBR, CBR-16 and the best overall response.

The number and percentage of patients in each analysis set will be summarized.

7.3 Disposition of Subjects

Study information including the date first subject signed ICF, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint of PFS, MedDRA version, WHO Drug version and SAS Version will be generated in a summary table. The date of last procedure for PFS is the date of progressive disease or death, otherwise use the date of the last response assessment.

The disposition of patients includes the number and percentage of patients for the following categories: randomized and not treated, discontinued study drug, primary reason to discontinue study drug, ongoing (if applicable at the time of DB lock), discontinued from the study, and primary reason to discontinue from the study (including deaths). All percentages will be based on the number of patients in the full analysis set.

In addition, the number and percentage of patients in the everolimus arm who crossed over to receive MLN0128 or MLN0128 + MLN1117 will be summarized.

7.4 Demographic and Other Baseline Characteristics

Summaries of demographics, baseline characteristics and stratification factors will be presented for subjects in the full analysis set.

The demographic characteristics consist of:

- Age (continuous)
- Age category 1
  - < 65 years
  - ≥ 65 years
- Age category 2
  - Adults (18-64 years)
  - From 65 to 84 years
  - 85 years and over
- Sex
- Height (cm)
- Weight (kg) – screening if available otherwise C1D1
- Ethnicity
- Race
- Geographic Region, Country, Site

  North America (Canada, United States)

  Europe (Czech Republic, France, Hungary, Italy, Poland, Russia, Spain, United Kingdom)

Baseline characteristics consist of:

- Time since initial diagnosis (months) [date of first dose – date of initial diagnosis/(30.4375))]
- Disease subtype [Clear Cell Renal Cell Carcinoma; Multilocular Cystic Renal Cell Carcinoma; Other histology with clear-cell component]
- Histopathology Variants [e.g. Renal Cell Carcinoma Associated with Neuroblastoma; Papillary Renal Cell Carcinoma, etc.]
- Disease stage at study entry [II; III; IV; Other; Unknown]
- Von Hippel-Lindau Syndrome status [Positive; Negative; Unknown]
- Von Hippel-Lindau Syndrome Positive status [PTEN; VHL; Other, Specify]
- Karnofsky Performance Status (KPS)

Stratification factors consist of:

- Prior lines of therapy: 1, >1 prior line
- International Metastatic Renal Cell Carcinoma Database Consortium risk category: Favorable, Intermediate, or Poor.

There will be separate summaries for stratification by original IRT and corrected IRT.

7.5 Medical History and Concurrent Medical Conditions

No summary for medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

No summary for medical history.

The number and percentage of patients taking concomitant medications will be tabulated by WHO standardized medication name based on safety analysis set. Concomitant medications are medications ongoing at the time of the first dose of study drug or medications that started after first dose and within 30 days of the last dose of study drug.

7.6.1 Prior Therapies

The number and percentage of patients with prior radiation, and prior anti-cancer therapies will be summarized based on safety analysis set. The following will be summarized for those patients with prior anti-cancer therapies:

- Number of prior lines
- Number of prior VEGF-targeted therapy
- Type of prior VEGF-targeted therapy
- Other types of prior treatments (non VEGF-targeted therapy) e.g. cytokines (eg, interleukin-2, interferon-alpha), monoclonal antibodies, (eg, bevacizumab, anti-PD-1),
- Best response to most recent prior therapy

7.6.2 Follow-up Anti-cancer Therapy

Number and percentage of patients receiving any anti-cancer therapy, and type of anti-cancer therapy will be summarized based on safety analysis set.

7.7 Study Drug Exposure and Compliance

7.7.1 Study Treatments

Cycles consist of 28 days for all treatment arms. In Treatment Arm A, everolimus will be administered 10 mg QD (every day of a 28-day treatment cycle). In Treatment Arm B, 30 mg of 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 4 mg and MLN1117 200 mg 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.

7.7.2 Extent of Exposure

Summaries and descriptive statistics of duration of treatment in weeks ((last dose date – start dose date + 1)/7), total number of cycles administered, average daily dose for everolimus, cumulative dose for each study drug, planned cumulative dose for each study drug and relative dose intensity will be summarized by treatment arm for patients in the safety analysis set.

Number of cycles administered = A treated cycle is defined as a cycle in which the patient received any amount of study drug. This is defined as Actual Dose greater than zero for at least one of the dosing days in the cycle for any study drug.

Cumulative dose (mg) = Sum of all doses (mg) administered to a subject during the treatment period.

Relative dose intensity = (cumulative dose / planned cumulative dose.

Everolimus treatment (10 mg QD)

Average daily dose (mg/day) is defined as:

Cumulative dose) / duration of treatment in days

Planned cumulative dose: (Date of first dose in last cycle – Date of first dose + 28 days) * 4 mg/day

MLN0128 treatment (30 mg QW)

Planned cumulative dose:

[(Date of first dose in last cycle – Date of first dose + 28 days) / 7] * 30 mg/week

MLN0128+MLN1117 treatment (QDx3)

Planned cumulative dose for MLN0128 4 mg QDx3:

[(Date of first dose in last cycle – Date of first dose + 28 days) / 7] * 12 mg/week

Planned cumulative dose for MLN1117 200 mg QDx3:

[(Date of first dose in last cycle – Date of first dose + 28 days) / 7] * 600 mg/week

7.7.3 Action on Drug

Action on study drug will be summarized by each cycle (Cycles 1-8) and total, for each treatment arm in the safety analysis set.

7.8 Efficacy Analysis

The analysis of PFS, OS and TTP will be based on the full analysis set. The analysis of ORR, CBR and CBR-16 will be based on both safety and response-evaluable analysis set. All efficacy analyses are based on the investigator response assessment per RECIST 1.1 criteria.

7.8.1 Primary Efficacy Endpoint(s)

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. Progression is based on the investigator response assessment per RECIST 1.1 criteria. PFS in months is defined as:

PFS (months) = (earliest date of progression or death – date of randomization + 1)/30.4375

In the event of progression, the date of progression is defined as the earliest date among target lesions, non-target and new lesions dates at that particular visit. 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 approach for handling of missing response assessments and censoring is presented below:

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Randomization	Censored
No post baseline tumor assessment and no death	Randomization	Censored
Disease progression documented between scheduled visits	Date of first documented disease progression	Progressed
Disease progression documented subsequent to missing 2 or more adequate tumor assessments	Date of first documented disease progression	Progressed
No documented disease progression or no death	Date of last adequate assessment	Censored
Alternate subsequent therapy started prior to disease progression	Date of last adequate assessment prior to the start of subsequent therapy	Censored
Death without progression and without subsequent anti-cancer therapy	Date of death	Progressed

Adequate Assessments: Investigator response assessment other than not evaluable, no assessment performed or missing (i.e. CR, PR, SD or PD).

PFS Analysis

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% confidence intervals (CIs) based on Brookmeyer and Crowley, and Kaplan-Meier estimates with 95% CIs at 6 and, 12 months 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 95% CI) estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates will be presented for comparison of everolimus vs. MLN0128 and everolimus vs. MLN0128 + MLN1117.

The stratification factors are 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). The original IRT stratification factors will be used in models.

The source of progression (death or progressive disease) will be summarized by treatment group.

The reasons for censoring in the PFS Kaplan-Meier analysis will be tabulated for each treatment group:

- Received subsequent anti-cancer therapy
- No baseline or no post baseline response assessment
- Death or progression after more than 1 missed visit
- Withdrawal of consent
- Lost to follow-up
- No documented death or disease progression

Subgroup Analyses

The analysis of PFS will be repeated in each of the following subgroups. The focus of the subgroup analyses is to assess the consistency of treatment effects and to present number of patients with events/censored, 25th, median and 75th percentile with HR and 95% CI within each subgroup for the 2 comparisons: everolimus vs. MLN0128 and everolimus vs. MLN0128+MLN1117. In addition, number of events/number of patients in each arm, hazard ratio (HR) and 95% CI within each subgroup for the 2 treatment comparisons will be presented as part of the forest plots and individual Kaplan-Meier survival curves for each subgroup will be presented.

The analysis of PFS will be repeated in each of the following subgroups.

- Stratification factors per IRT (original):
- Number of prior lines of therapy (1, >1 prior line)
- International Metastatic Renal Cell Carcinoma Database Consortium risk category (Favorable, Intermediate, or Poor)

7.8.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include OS, ORR, TTP, CBR with SD of any duration and CBR with SD duration of at least 4 months (CBR-16). The analyses of OS and TTP will be done for the full analysis set. The analyses of ORR, CBR, and CBR-16 will be done for both the safety and response evaluable set.

In the event of response (i.e. overall response is PR or better), the date used for the start of response is defined as the latest of all dates among target lesions or non-target lesions dates at that particular visit.

Overall survival (OS)

Overall survival in months is defined as the time from the date of randomization to the date of death (OS (months) = (date of death – date of randomization + 1)/30.4375). Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. The Kaplan-Meier method will be used to analyze the distribution of OS for each treatment arm. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs), and Kaplan-Meier estimates with 95% CIs at 6 and 12 months will be presented. A stratified log-rank test and hazard ratios (and 95% CI) estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates will be presented for the comparison of everolimus to MLN0128 and everolimus to MLN0128+MLN1117. The stratification factors are 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). The original IRT stratification factors will be used in models.

Best Overall Response

Best overall response is defined as the best response recorded after the first dose of study drug until subsequent therapy.

Best Overall Response (unconfirmed): This will be the best response reported by the investigator; ordered from best to worst: Complete Response, Partial Response, Stable Disease, Progressive Disease. The best response can also be Not Evaluable (NE) or No assessment performed if this is the only investigator assessment of objective response available for the patient.

Best Overall Response (confirmed): This will be the best response reported by the investigator; ordered from best to worst: Complete Response, Partial Response, Stable Disease, Progressive Disease. Complete or partial responses may be claimed as best response only if the criteria for each are met at a subsequent time point. For the best overall response (confirmed), the confirmation derivation rules will be as described in the following table.

Overall response 1st time point	Overall response subsequent time point	BEST overall response
CR	CR	CR
CR	PR	PR
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD
PR	NE	SD
NE	NE	NE

Note: No adjustment for a minimum criteria for SD is needed as the first protocol scan is at the end of cycle 2, approximately 8 weeks from first dose.

Overall response rate (ORR) is defined as the proportion of patients among response evaluable analysis set who achieve a best overall response of CR or PR based on investigators assessment of response following RECIST 1.1. ORR will be summarized by both ORR based on unconfirmed best response and ORR based on confirmed best response. A stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors will be used to compare ORR between treatment arms based on the original IRT (everolimus vs. MLN0128 and everolimus vs. MLN0128+MLN1117). The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each comparison specified above based on original IRT.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients who achieve a best response of CR, PR, or SD of any duration. CBR will be presented for both CBR based on unconfirmed best response and CBR based on confirmed best response. A stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors will be used to compare CBR between treatment arms (everolimus vs. MLN0128 and everolimus vs. MLN0128+MLN1117). The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each comparison specified above.

Clinical Benefit Rate with SD duration of at least 4 months (CBR-16)

CBR with SD duration of at least 4 months (CBR-16) is defined as the proportion of patients who achieve CR or PR of any duration or have SD with duration of at least 16 weeks (see below). CBR-16 will be summarized based on unconfirmed best response and confirmed best response. A stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors will be used to compare CBR-16 between treatment arms (paclitaxel vs. paclitaxel+MLN0128,

paclitaxel vs. MLN0128 and paclitaxel vs. MLN0128+MLN1117). The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each comparison specified above.

SD for at least 16 weeks is a subset of SD, only calculated for those patients with a best response of SD. It is defined as SD at the end of Cycle 2 and at the end of Cycle 4. In addition, to account for unscheduled visits or PFS follow up visits (for those who discontinued for reasons other than progressive disease prior to alternative therapy or cross-over) SD for at least 16 weeks will include cases where two or more post baseline scans have SD (or PR/SD for confirmed response) and the duration of stable disease is greater than 112 days.

CBR at 16 weeks (unconfirmed) is defined as the number of patients who achieve CR or PR at any time or have SD for at least 16 weeks.

CBR at 16 weeks (confirmed) is defined as the number of patients who achieve confirmed CR or confirmed PR at any time or have SD for at least 16 weeks or meet the following criteria:

Overall response at end of Cycle 2	Overall response at end of Cycle 4	Meet criteria CBR at 16 weeks?
CR/PR (unconfirmed)	SD	YES
SD	CR/PR (unconfirmed)	YES

In addition, the proportion of patients with the following best response will be summarized by treatment group: CR, PR, SD, SD at least 16 weeks, overall response (ORR), CBR and CBR-16 weeks.

Time to Tumor Progression (TTP)

TTP in months is defined as the time from the date of randomization to the date of first documentation of progression (TTP (months) = (date of first documentation of progression – date of randomization + 1)/30.4375). For a patient whose disease has not progressed, TTP will be censored at the last response assessment that is SD or better.

The Kaplan-Meier method will be used to analyze the distribution of TTP for each treatment arm. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs), and Kaplan-Meier estimates with 95% CIs at 6and 12 24 months will be presented. A stratified log-rank test and hazard ratios (and 95% CI) estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates will be presented for comparison of everolimus to MLN0128 and everolimus to MLN0128+MLN1117. The stratification factors are 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). The original IRT stratification factors will be used in models.

7.8.3 Additional Efficacy Endpoint(s)

The duration of objective response (DOR) will be calculated for those patients with a best response of CR or PR (for unconfirmed), and is defined as the number of days from the start date of CR, or PR (whichever response is achieved first) until progressive disease or until the last adequate response assessment if there is no progressive disease. The Kaplan-Meier method will be used to analyze the distribution of DOR for each treatment arm. The 25th, 50th (median), and 75th percentiles, along with median and 2-sided 95% confidence intervals (CIs) will be presented. The analysis of duration of response will be descriptive in nature and will be based on response-evaluable analysis set.

Waterfall plots of the best percentage change from baseline in the sum of the longest diameter (SLD) of the target lesions will be generated for each treatment group using the response-evaluable analysis set. If one of the target lesion measurements is missing at a visit then the SLD at that visit will not be used for selecting the best percentage change from baseline in SLD for the waterfall plot. The SLD will be calculated based on the following rules:

1. If a target lesion at a visit is "too small to measure", per the CRF completion guidelines the value of 5 mm should have been entered as the diameter. This would be used to calculate the SLD.
2. If 2 target lesions conjoin into a single lesion (status="coalesce"), per the CRF completion guidelines the LD of the resulting merged lesion is divided by 2 and reported in the CRF for each of the previous TL and then would be included in the SLD.
3. If a target lesion splits into 2 lesions (status="split"), the LDs of the fragmented portions are added up and reported in the CRF and would be included in the SLD.
4. Sum of the target lesions (SLD) [in mm] is defined as the sum of the longest diameters of all target lesions at each visit.
5. SLD change from baseline at visit x [in mm] is defined as the absolute change in the SLD from baseline to each visit = "SLD at visit x" – "SLD at baseline". Baseline SLD corresponds to the SLD from the screening visit.
6. Percentage change from baseline in SLD [in %] is defined as "SLD change from baseline at visit x" / "SLD at baseline" * 100.
7. Best percentage change in SLD is defined as the percentage change from baseline in SLD at the visit with the smallest SLD value among all the post screening visits.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic 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 the population PK analysis will be presented in a separate report.

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7.10 Patient Reported Outcomes

Patient-reported outcome (PRO) assessments will be collected through 2 different instruments: EORTC QLQ-C30 and FKSI-DRS. The full analysis set will be used to present patient-reported outcome analysis. For each treatment group and at each assessment point and overall, the number and percentage of compliance for the EORTC QLQ-C30 and FKSI-DRS will be summarized. Compliance is defined as the number of questionnaires completed (answered at least one question) as a proportion of the number of expected questionnaires per the schedule of events (Day 1 of each cycle and End of Treatment). Patients who died will not be included in the expected count.

Patient with missing baseline scores are not assessable for baseline description or change from baseline. Patients with baseline scores, but with no follow-up scores, are not assessable for change from baseline. Published manuals/guidance for EORTC QLQ-C30 will be used for scoring and handling missing data. In the case where there is no guidance for handling missing data, missing items will be considered missing, they will not be imputed.

7.10.1 EORTC QLQ-C30 and FKSI-DRS Score

Descriptive statistics (including 95% CI around mean) for actual values and the change from baseline (post – baseline) will be tabulated at each scheduled time point and the EOT visit for each of the functional and symptom scores from the EORTC QLQ-C30 and FKSI-DRS questionnaires, the global health status/QOL score and summary score from the EORTC QLQ-C30 questionnaire, and the FKSI-DRS summary score up to 6 cycles (extend beyond 6 cycles if at least 10 patients in each treatment arm have results). In addition, the mean and mean change from baseline (including 95% CI) will also be presented over time by treatment group in figures up to 6 cycles (extend beyond 6 cycles if at least 10 patients in each treatment arm have results).

The change from baseline of EORTC QLQ-C30 subscales, global health status/QOL, summary score,FKSI-DRS subscales, and summary score will be analyzed using linear mixed models, including treatment group, visit, the interaction between treatment group and visit, baseline score (and other covariates i.e. stratification factors as per original IRT) as covariates. Random-intercept only model with appropriate covariance structure will be used based on the following covariance structure in order from unstructured, spatial-power and AR(1). The first covariance structure that has all the parameter estimates converged for all the subscales will be used. The estimated means with 95% CIs will be provided at each time point up to 6 cycles for each treatment arm (extend beyond 6 cycles if at least 10 patients in each treatment arm have results). The mean difference in each score and 95% CIs and p values for the pairwise comparison of everolimus to MLN0128 and everolimus to MLN0128+MLN1117 will be presented at each time point up to 6 cycles (extend beyond 6 cycles if at least 10 patients in each treatment arm have results).

7.11 Safety Analysis

All safety analyses will be performed using the Safety analysis set.

7.11.1 Adverse Events

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.

Treatment-emergent AEs 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.

Treatment emergent adverse events will be summarized based on the number and percentage of patients experiencing events by MedDRA system organ class and preferred term. Tabular summaries by MedDRA system organ class and preferred term will be provided for the following:

- Treatment-emergent adverse events.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- Most commonly reported TEAEs (at least 10% in any arm, sorted by preferred term).
- Serious adverse events.
- Most frequent non-serious TEAEs (≥ 5% in any arm)

Patients reporting the same event more than once will have that event counted only once within each body system, and once within each preferred term.

Adverse events of interest will be tabulated for the following:

Adverse event of interest	MedDRA Preferred Term	
Asthenic Conditions	Asthenia, Decreased activity, Fatigue, Malaise, Sluggishness (modified HLT)	
Mucosal Inflammation	Enanthema	Allergic stomatitis
	Mucosa vesicle	Aphthous ulcer
	Mucosal atrophy	Lip erosion
	Mucosal discolouration	Lip ulceration
	Mucosal dryness	Mouth ulceration
	Mucosal erosion	Oral mucosa erosion
	Mucosal exfoliation	Palatal ulcer
	Mucosal haemorrhage	Stomatitis
	Mucosal hyperaemia	Stomatitis haemorrhagic
	Mucosal hypertrophy	Stomatitis necrotising
	Mucosal induration	
	Mucosal inflammation	
	Mucosal membrane hyperplasia	
	Mucosal necrosis	
	Mucosal pain	
	Mucosal pigmentation	
	Mucosal roughness	
	Mucosal toxicity	
	Mucosal ulceration	
	Mucous membrane disorder	
	Oedema mucosal	
	Mucosal infection	
	Mucosal excoriation	
	Erythroplasia	
	Burning sensation mucosal	
	Paraesthesia mucosal	
	Leukoplakia	
	Drug eruption	
	Fixed eruption	
	Mucocutaneous haemorrhage	
Rash	Mucocutaneous rash	
	Nodular rash	
	Rash	
	Rash erythematous	
	Rash generalised	
	Rash macular	
	Rash maculo-papular	
	Rash maculovesicular	

Adverse event of interest	MedDRA Preferred Term
	Rash morbilliform Rash papular Rash rubelliform Rash scarlatiniform Rash vesicular

7.11.1.1 Deaths

All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status). On-study death is defined as death that occurs between the first dose of study drug and 30 days after the last dose of study drug (adverse events with an outcome of death).

All cause mortality will be tabulated, which includes death of all causes, deaths related to disease under study, and deaths due to other reasons. On-study deaths will be tabulated, which includes deaths related to disease under study, deaths due to other reasons, and deaths within 30 and 60 days of first dose.

7.11.1.2 Clinical Laboratory Evaluations

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE version 4.03. The number and proportion of patients with shifts in NCI CTCAE toxicity grades relative to the baseline toxicity grade will be summarized for the following laboratory tests:

- Hematology: Hemoglobin increased, Activated partial thromboplastin time (aPTT) prolonged, INR increased, Lymphocyte count decreased, Lymphocyte count increased, Neutrophil count decreased, Platelet count decreased, White blood cell count decreased
- Chemistry: Alanine aminotransferase (ALT) increased, Alkaline phosphatase increased, Aspartate aminotransferase (AST) increased, Bilirubin (total) increased, Cholesterol high, Creatinine increased, Gamma glutamyl transferase (GGT) increased, Corrected Calcium - decreased, Corrected Calcium – increased, Glucose – decreased, Glucose – increased, Potassium – decreased, potassium – increased, magnesium – decreased, magnesium – increased, sodium – decreased, sodium – increased, triglycerides – increased, albumin – decreased, phosphate – decreased, amylase – increased

The shift from baseline to worst post baseline will include scheduled and unscheduled visits.

For fasting glucose, the shifts from baseline to the worst post baseline (2 hours only) will be summarized for the everolimus and MLN0128 + MLN1117 arms, and for the MLN0128 QW patients enrolled prior to protocol amendment no 4. Similarly, the changes from pre-dose to 2 hours post dose fasting glucose values will be presented.

The actual values (in SI units) and change from baseline in clinical laboratory parameters will be summarized by treatment group for Neutrophils (ANC), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Glucose, Hemoglobin A1c, Cholesterol (total), Triglycerides,

High-density lipoprotein cholesterol (HDL-C) and Low-density lipoprotein cholesterol (LDL-C) at each scheduled visit up to and including 6 cycles. Figures of mean actual values over time will also be generated for these clinical laboratory parameters (in SI units).

7.11.2 Vital Signs

The actual values of vital sign parameters including temperature, heart rate, systolic and diastolic blood pressure, and weight, will be summarized by treatment group at each scheduled visit up to and including 6 cycles. Change from baseline will also be presented.

7.11.3 12-Lead ECGs

The actual values and change from baseline for ECG results (QT, QTcF, PR interval, QRS interval, Ventricular Rate) will be summarized over time for each treatment group up to 6 cycles. In addition, the number and percent of patients with increases >30 ms and >60 ms from pre-dose in QTcF will also be summarized over time up to 6 cycles.

All QT values will be converted to QTcF using Fridericia's correction:

$$QT_F = \frac{QT}{\sqrt[3]{RR}} \text{ (sec)}$$

[Note: RR (sec) = 60 / ventricular rate in beats/minute].

7.11.4 Karnofsky Performance Status

Shifts from baseline to the worst post-baseline on study score will be tabulated by treatment arm.

7.12 Interim Analysis

As specified in the protocol

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.

A second futility analysis not specified in the protocol was to be performed when 50% of PFS events occurred for each of the pairwise comparisons: everolimus vs. MLN0128 QW and everolimus vs. MLN0128 + MLN1117. The decision rule is based on a Bayesian framework: posterior probability (true HR > 0.74 | observed HR) is greater than 80%. The futility criteria will be met if the observed PFS HR for either comparison is greater than or equal to 0.945.

7.13 Crossover Treatment

Data collected after crossover treatment begins will not be included in the planned efficacy and safety analyses for the study.

The following information will be provided in a listing for crossover patients from the everolimus arm (presented by crossover treatment):

- Duration of treatment (weeks) prior to/after crossover

In addition, TEAEs resulting in discontinuation of crossover treatment, serious AEs, and deaths while on cross-over treatment will be presented in by-patient listings.

7.14 Changes in the Statistical Analysis Plan

1. Based on the results from the planned interim analysis (after the first 30 patients in each arm had received 2 cycles of study drug) enrollment to the study was permanently closed in all treatment arms. Therefore, the main analysis will no longer be conducted when the required number of PFS events has been reached. The final analysis may be conducted when all patients have received at least 6 cycles of treatment or later.
2. For PFS analysis, patients who started alternate subsequent therapy prior to disease progression will be censored at the date of last adequate assessment prior to the start of subsequent therapy. The protocol did not explicitly state this condition.
3. In addition to Kaplan-Meier method that will be used to analyze distribution of PFS, OS and TTP for each treatment arm and the p-values from a stratified log-rank test, the HRs and 95% CIs from a stratified Cox regression model with treatment arm and stratification factors as covariates will also be presented for comparison of everolimus to MLN0128 and everolimus to MLN0128+MLN1117. The protocol did not explicitly state the model for estimating the HRs.
4. For secondary endpoints e.g. ORR, CBR, and CBR-16 will be based on both confirmed and unconfirmed best overall response.

8.0 REFERENCES

1. 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.

9.0 APPENDIX

Appendix A By-Subject Listings

In addition to the analysis outputs outlined above in the main text, separate by-patient listings will also be generated to include the following information:

- Disposition of subjects (including crossover treatment, if applicable)
- Demographic and other baseline characteristics (including stratification factors)
- Concomitant medications
- Follow-up anti-cancer therapy
- TEAEs resulting in discontinuation of study drug
- TEAEs resulting in discontinuation of crossover treatment
- SAEs
- SAEs for crossover patients
- Deaths and cause of death
- Deaths and cause of death for crossover patients
- Sparse PK data
- RECIST response assessment and best overall response based on investigator assessment
- Important protocol deviations

Appendix B Date Imputation Rules

Incomplete Dates in the Screening Period

1. If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
2. If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.
3. If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used.

Incomplete Adverse Event Onset Date

Assumption: For on-study Adverse Events.
If *year* is missing (or completely missing): set to the date of first dose.
If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):
If *year* = year of first dose: set the date to the first dose date.
If *year* < year of first dose: set *month* and *day* to December 31st.
If *year* > year of first dose: set *month* and *day* to January 1st.
If *month* and *year* are present and *day* is missing:
If *year* = year of first dose, and:
If *month* = month of first dose: set *day* to day of first dose.
If *month* < month of first dose: set *day* to last day of *month*.
If *month* > month of first dose: set *day* to 1st day of *month*.
If *year* < year of first dose: set *day* to last day of month.
If *year* > year of first dose: set *day* to 1st day of month.
For all other cases: set to date of first dose.

Incomplete Concomitant Medication Start Date

If *year* is missing (or completely missing): do not impute.
If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):
Set *month* and day to January 1st.
If *year* and *month* are present and *day* is missing:
Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

If *year* is missing (or completely missing): do not impute.
If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):
Set *month* and day to December 31st.
If *year* and *month* are present and *day* is missing:
Set *day* to last day of the month.

Incomplete Subsequent Anti-Cancer Therapy Start Date

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of last dose of study treatment +1

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose.

Otherwise set the imputed date to date of last dose + 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	04-Dec-2018 15:54 UTC
	Biostatistics Approval	04-Dec-2018 15:54 UTC
	Biostatistics Approval	04-Dec-2018 16:19 UTC