Title: A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/ HER2 Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant

NCT Number: NCT02049957

SAP Approve Date: 23 July 2018

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C31001

A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2- Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant

PHASE 1/2

Version**:** Final

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Prepared by:

PPD

Based on:

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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

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{24}	area under the plasma concentration versus time curve from zero to 24 hours
AUC_t	area under the plasma concentration versus time curve from zero to the last measurable concentration
CBR	clinical benefit rate
CBR-16	clinical benefit rate at 16 weeks
CBR-24	clinical benefit rate at 24 weeks
CI	confidence interval
C_{max}	single-dose maximum (peak) concentration
CR	complete response
CT	computed tomography
CTC	circulating tumor cell
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment (visit)
ER	estrogen receptor
ER+/HER2−	estrogen receptor positive/human epidermal growth factor receptor-2 negative
HER2	human epidermal growth factor receptor 2
IM	intramuscular; intramuscularly
IV	intravenous; intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	progesterone receptor
PT/INR	prothrombin time/international normalized ratio
QD	*quaque die*; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum [of] longest diameters
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse events
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
US	United States
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

Phase 1b

- To evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

Phase 2

- To evaluate the antitumor activity by CBR at 16 weeks (CBR-16 is defined as the proportion of patients who achieve CR or partial response of any duration or have SD at 16 weeks) of treatment with MLN0128 in combination with either exemestane or fulvestrant.

4.2 Secondary Objectives

- To further evaluate the antitumor activity of MLN0128 in combination with either exemestane or fulvestrant.
- To evaluate the pharmacokinetics of MLN0128 and exemestane when administered in combination and to evaluate the pharmacokinetics of MLN0128 when administered in combination with fulvestrant.
- To assess the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

4.3 Exploratory Objectives

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[redacted]

4.4 Study Design

This is a phase 1b/2 study of the safety and efficacy of MLN0128 in combination with exemestane or fulvestrant therapy in women with ER+/HER2– advanced or metastatic breast cancer that has progressed on treatment with everolimus in combination with exemestane (any country) or fulvestrant (US only). Patients enrolled in this study will continue taking the same

prior therapy (either exemestane or fulvestrant) at their established dose, in combination with MLN0128.

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. MLN0128 will be administered in 28-day treatment cycles.

4.4.1 Phase 1b

In the phase 1b portion of the study, the safety and tolerability of MLN0128 using a capsule formulation based on unmilled (Part 1) and milled (Part 2) active pharmaceutical ingredient (API) in combination with either exemestane (any country) or fulvestrant (US only) will be evaluated. Patients enrolled in Part 1 will remain on MLN0128 capsules based on unmilled API. Patients will be enrolled as follows:

Part 1 (Capsules Based on Unmilled API):

MLN0128 + Exemestane Safety Cohort: Six patients will receive MLN0128 capsule formulation based on unmilled API (5 mg QD) in combination with exemestane (administered per prior therapy for the patient). Steady-state serial PK samples will be collected to quantify both MLN0128 and exemestane to characterize the PK of MLN0128 and exemestane when administered in combination.

MLN0128 + Fulvestrant Safety Cohort (US Only): Six patients will receive MLN0128 capsule formulation based on unmilled API (5 mg QD) in combination with high-dose fulvestrant (500 mg IM every month). After completing 2 cycles of treatment with MLN0128 (Cycle 2, Day 28) in combination with fulvestrant, a safety and tolerability assessment will be performed. If ≥2 DLTs occur in either treatment group (exemestane or fulvestrant) after completing 2 cycles of treatment with MLN0128 (5 mg QD), the dose of MLN0128 will be reduced in that treatment group (MLN0128 in combination with exemestane or MLN0128 in combination with fulvestrant) to 4 mg QD for patients subsequently enrolled in the phase 2 portion study.

Part 2 (Capsules Based on Milled API):

MLN0128 + Exemestane (Any Country)/Fulvestrant (US Only) Safety Cohort 1: Six patients will receive MLN0128 capsule formulation based on milled API (3 mg once daily [QD]) in combination with either exemestane or fulvestrant. Serial blood samples will be collected to evaluate the PK of MLN0128 when administered in combination with either exemestane or fulvestrant. After the last patient completes Cycle 1, a safety and tolerability assessment will be performed. If ≥ 2 dose-limiting toxicities (DLTs) occur in these 6 patients, the dose of MLN0128 will be reduced to 2 mg QD for patients subsequently enrolled in Cohort 2 of Part 2 of the phase 1b portion of this study. If ≤1 DLT occurs in Cohort 1, the dose of MLN0128 will be escalated to 4 mg QD for patients entering Cohort 2.

MLN0128 + Exemestane (Any Country)/Fulvestrant (US Only) Safety Cohort 2: Six patients will receive MLN0128 capsule formulation based on milled API, either 4 or 2 mg QD based on the safety observed in Cohort 1, in combination with either exemestane or fulvestrant. Serial PK samples will be collected as outlined for Cohort 1. After the last patient completes Cycle 1, a safety and tolerability assessment will be performed.

4.4.2 Phase 2

In the phase 2 portion of the study, the safety and efficacy of MLN0128 in combination with either exemestane (any country) or fulvestrant (US only) will be evaluated. Patients will be administered MLN0128 at either 4, 3, or 2 mg QD in combination with either exemestane (any country) or fulvestrant (US only), depending on the outcome of the safety and tolerability analysis performed in the phase 1b portion of the study.

Another safety and tolerability assessment will be performed during the phase 2 portion of the study where the first 6 patients treated with MLN0128 (either 4 mg, 3, mg, or 2 mg QD) in combination with exemestane or fulvestrant who have completed 2 cycles of treatment with MLN0128 will be evaluated for TEAEs. Enrollment of patients into the study will continue during this safety and tolerability assessment.

Patients will be enrolled into one of 2 parallel cohorts, depending on the quality and/or duration of their prior response to everolimus in combination with either exemestane (any country) or fulvestrant (US only) as follows:

Everolimus-Resistant Cohort: This is a cohort of 56 response-evaluable patients who have progressed on treatment with everolimus in combination with either exemestane (any country) or fulvestrant (US only) without achieving an objective response (CR or partial response) or after achieving SD for <6 months as their best response. Patients will receive MLN0128 in combination with the same dose of the previously administered treatment (exemestane [any country] or fulvestrant [US only]).

Everolimus-Sensitive Cohort: This is a cohort of 48 response-evaluable patients who have progressed on treatment after achieving a CR or partial response of any duration, or SD ≥6 months with prior everolimus treatment in combination with either exemestane (any country) or fulvestrant (US only). Patients will receive MLN0128 in combination with the same dose of the previously administered treatment (exemestane [any country] or fulvestrant [US only]).

Sparse PK samples will be collected from all patients enrolled in the study (regardless of whether they are administered MLN0128 in combination with exemestane or fulvestrant) for plasma PK analysis of MLN0128 only. Data generated in this study will be combined with data from other studies in which the PK of MLN0128 is characterized for population PK analysis.

Radiological tumor evaluations (CT scan with intravenous [IV] contrast or magnetic resonance imaging [MRI] as clinically indicated) of the chest, abdomen, and pelvis) will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1). Throughout the study, 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. Adverse events will be assessed, clinical laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

5.0 ANALYSIS ENDPOINTS

The primary endpoints include:

Phase 1b

- Adverse events, SAEs, assessments of clinical laboratory values, vital sign measurements, physical examination findings, and electrocardiograms (ECGs).

Phase 2

- CBR-16.

5.1 Secondary Endpoints

The secondary endpoints include:

- Clinical benefit rate at 24 weeks (CBR-24 is defined as the proportion of patients who achieve CR or partial response of any duration or have SD at 24 weeks).
- Overall response rate (ORR; defined as best response of CR or partial response).
- Progression-free survival (PFS).
- Overall survival (OS).
- Change in tumor size from baseline.
- Steady-state PK parameters of MLN0128 and exemestane including, but not limited to, single-dose maximum (peak) concentration (Cmax), Tmax, area under the plasma concentration versus time curve from zero to 24 hours (AUC24h), area under the plasma concentration versus time curve from zero to the last measurable concentration (AUCt), and t1/2.
- Adverse events, SAEs, assessments of clinical laboratory values, vital sign measurements, physical examination findings, and ECGs.

5.2 Exploratory Endpoints

The exploratory endpoints include:

CCI

[redacted]

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Phase 1b

The safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant will be evaluated. Patients will be enrolled as follows:

- In Part 1 of the phase 1b portion of the study, up to 6 patients will be enrolled into the MLN0128 + Exemestane Safety Cohort and up to 6 patients will be enrolled into the MLN0128 + Fulvestrant Safety Cohort. The number of patients is based on clinical considerations.
- In Part 2 of the phase 1b portion of the study, 6 patients will be enrolled into MLN0128 + Exemestane/Fulvestrant Safety Cohort 1, and 6 patients will be enrolled into MLN0128 + Exemestane/Fulvestrant Safety Cohort 2. The number of patients is based on clinical considerations.

Phase 2

The sample size for each cohort in the phase 2 portion of the study is based on a standard Simon two-stage design. A Bayesian predictive probability design was used to allow multiple interim analyses to stop early for futility [1]. See Section 6.0 for sample size assumptions. Up to 56 response-evaluable patients will be enrolled in the Everolimus-Resistant Cohort. In the Everolimus-Sensitive Cohort, up to 48 response-evaluable patients will be enrolled.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

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

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. Cycle 1 day 1 values are considered pre-dose. Screening values are used for baseline values if a cycle 1 day value is unavailable.

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.

For the categorical variables, the count and proportions of each possible value will be tabulated. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. Additional statistics will be tabulated for pharmacokinetic data (see Section 7.9.1).

A month is operationally defined to be 30.4375 days.

7.1.1 Data Presentation

Results from the phase 1b and phase 2 portions of the study will be presented separately as follows (unless specified elsewhere):

Phase 1b:

1. Baseline tables (demographics, disease characteristics, prior therapies)

Part 1 MLN0128 Unmilled API			Part 2 MLN0128 Milled API			Phase 1b Total
MLN0128 5 mg QD + Exemestane N=6	MLN0128 5 mg QD+ Fulvestrant N=6	Total N=12	MLN0128 3 mg QD + Exemestane/ Fulvestrant N=6	MLN0128 4 mg QD + Exemestane/ Fulvestrant N=6	Total N=12	N=24

2. Disposition, Safety

Part 1 MLN0128 Unmilled API			Part 2 MLN0128 Milled API					Phase 1b Total
MLN0128 5 mg QD + Exemestane N=6	MLN0128 5 mg QD+ Fulvestrant N=6	Total N=12	MLN0128 3 mg QD +Exemestane N=3	MLN0128 3 mg QD + Fulvestrant N=3	Total MLN0128 3 mg QD N=6	MLN0128 4 mg QD+ Exemestane N=6	Total N=12	N=24

Phase 2:

1. Disposition, Baseline and Demographic Characteristics, and Efficacy (no total needed)

Everolimus Sensitive Cohort			Everolimus Resistant Cohort			Total (except efficacy)
MLN0128 4 mg QD + Exemestane	MLN0128 4 mg QD + Fulvestrant	Sensitive Total	MLN0128 4 mg QD + Exemestane	MLN0128 4 mg QD + Fulvestrant	Resistant Total	

2. Safety

MLN0128 4 mg QD + Exemestane			MLN0128 4 mg QD + Fulvestrant			Total
Everolimus Sensitive Cohort	Everolimus Resistant Cohort	Total	Everolimus Sensitive Cohort	Everolimus Resistant Cohort	Total	

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Conventions for Partial Adverse Event/Concomitant Medication Dates

Missing or incomplete start dates will be imputed based on the algorithm described below:

If the start date has month and year but day is missing, the adverse event will be considered treatment-emergent or the therapy concomitant if both the month and year of the start date are on or after the month and year of the date of the first dose of MLN0128 and on or before the month and year of the date of the last dose of MLN0128 plus 30 days.

- If the start date has year, but day and month are missing, the adverse event will be considered treatment -emergent or the therapy concomitant if the year of the start date is on or after the year of the date of the first dose of MLN0128 and on or before the year of the date of the last dose of MLN0128 plus 30 days.

7.1.4 Conventions for Other Partial Dates

Missing or incomplete dates recorded during the screening visits (e.g date of initial diagnosis) will be imputed based on the algorithm described below:

- 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.
- 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 15th of January will be used.

- 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, unless other data indicates that the date is earlier.

7.2 Analysis Sets

7.2.1 Safety Population

Safety population: patients who receive at least 1 dose of study drug. All safety analyses will be performed using the safety population.

7.2.2 Response-Evaluable Population

Response-evaluable population (phase 2 only): patients who receive at least 1 dose of study drug and have measurable disease at baseline.

7.2.3 Pharmacokinetics Population

Pharmacokinetic population: patients with sufficient dosing and PK data to reliably estimate PK parameters. PK analyses will be performed using the PK population.

7.3 Disposition of Subjects

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, MedDRA Version, WHODrug Version, and SAS Version will be generated in a summary table.

For the phase 1 portion the number of patients in the safety population, in the pharmacokinetics population, and the reason study drug was discontinued will be summarized.

For the phase 2 portion the number of patients in the safety population, in the response-evaluable population, the dose level of exemestane or fulvestrant at study entry, the reason study drug was discontinued, and the end of study reasons will be summarized.

All percentages will be based on the number of patients in the safety population.

The number of subjects enrolled by region, country and site will be summarized:

North America
- United States

Europe
- Belgium
- France

7.4 Demographic and Other Baseline Characteristics

Summaries of demographic and baseline characteristics will be presented for subjects in the safety population.

The demographic characteristics consist of:

- Age at date of informed consent (continuous)
- Age category 1.
  - <65 years.
  - ≥65 years.
- Age category 2.
  - Adults (18-64 years).
  - From 65 to 84 years.
  - 85 years and over.
- Height (cm).
- Weight (kg) [at screening if available, otherwise use C1D1].
- Ethnicity.
- Race.

Baseline characteristics consist of:

- Baseline ECOG performance status.
- Histological subtype (Basal, Luminal A, Luminal B, Normal Breast-like).
- Time since initial diagnosis (months) [(date of first dose – date of initial diagnosis)/30.4375].
- Stage of disease at initial diagnosis.
- Number and percent positive for each marker: PR, C-myc amplification, BRCA1, BRCA2, and EGFR.
- Number and percent positive for PTEN (from tumor samples).

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 medication history.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO standardized medication name (generic name).

7.6.1 Prior Therapies

The number and percentage of patients with prior surgery, prior radiation, and prior antineoplastic therapies will be summarized. The following will be summarized for those patients with prior antineoplastic therapies:

- Prior therapy received (PTDECOD in PT dataset).
- Number of prior therapy regimens (PTGRPID in PT dataset).
- Best response to most recent prior therapy.

7.7 Study Drug Exposure and Compliance

7.7.2 Extent of Exposure

The overall treatment duration in weeks (date of last dose – date of first dose + 1/ 7), number of treated cycles (distribution and summary statistics), cumulative dose for each study drug, average daily dose in mg/day [cumulative dose in mg / duration of treatment in days] for MLN0128 and exemestane, planned cumulative dose for each study drug, and the relative dose intensity for each study drug will be summarized for patients in the safety population.

A treated cycle is defined as a cycle in which the patient receives any amount of MLN0128 (actual dose greater than zero for at least one of the dosing days in the cycle).

The cumulative dose for MLN0128 and exemestane in (mg) is the sum of all doses (mg) administered to a subject during the treatment period.

Relative dose intensity = [cumulative dose / planned cumulative dose] * 100.

For MLN0128 and exemestane the relative dose intensity is calculated as:
[cumulative dose in mg / assigned dose level (mg) at the start of the study * duration of treatment in days] * 100.

For fulvestrant the relative dose intensity is calculated as:
[cumulative dose in mg / assigned dose level (mg) at the start of the study * number of treatment cycles] * 100.

7.7.3 Action on Study Drug

The number and percentage of patients for the following actions on study drug for MLN0128, exemestane, and fulvestrant:

- Dose Reduced at Least Once.
- Dose Held at Least Once.
- Dose Missed at Least Once.
- Discontinued Permanently.

Action on study drug will be summarized by cycle (cycles 1-6) and overall for the safety population.

7.8 Efficacy Analysis

Phase 1b

Data listings will present the tumor measurements from CT or MRI, the sum of the long diameter (SLD), percent change from baseline in the SLD, percent change from nadir in the SLD, non-target disease assessment, new lesion assessment, disease response assessment by the investigator based on RECIST criteria, and if symptomatic deterioration occurred at each response assessment. In addition, the best overall response (unconfirmed and confirmed), duration of stable disease (SD), and duration of response will be presented in a data listing.

See Section 7.8.3 Additional Efficacy Endpoints for the definition of duration of stable disease and the duration of response.

7.8.1 Primary Efficacy Endpoint(s)

Phase 2

The primary efficacy endpoint for the phase 2 portion of the study is the clinical benefit rate at 16 weeks (CBR-16) and is defined as the proportion of patients who achieve CR or partial response of any duration, or have stable disease [SD] at 16 weeks.

The number and percentage of patients achieving clinical benefit at 16 weeks will be summarized by cohort and combination partner (Exemestane or Fulvestrant) within each cohort. The estimate of the CBR-16 will be presented with a 2-sided 95% exact binomial confidence interval. CBR-16 will be determined based on both unconfirmed and confirmed response (see Section 7.8.3 Additional Efficacy Endpoints for definitions) for the response-evaluable population.

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 (see exception below).

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
CR/PR (unconfirmed)	SD
SD	CR/PR (unconfirmed)

7.8.2 Secondary Efficacy Endpoint(s)

Phase 2

Clinical benefit rate at 24 weeks (CBR-24)

The CBR-24 is defined as the proportion of patients who achieve CR or partial response of any duration, or have SD at 24 weeks.

The number and percentage of patients achieving CBR-24 will be summarized by cohort and combination partner (Exemestane or Fulvestrant) within each cohort. The estimate of the CBR-24 will be presented with a 2-sided 95% exact binomial confidence interval. The CBR-24 will be determined based on both unconfirmed and confirmed best overall response (see Section 7.8.3 Additional Efficacy Endpoints for definitions) for the response-evaluable population.

SD for at least 24 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, Cycle 4, and Cycle 6 (see exception below).

CBR at 24 weeks (unconfirmed) is defined as the number of patients who achieve CR or PR at any time or have SD for at least 24 weeks.

CBR at 24 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 24 weeks or meet the following criteria:

Overall response at end of Cycle 2	Overall response at end of Cycle 4	Overall Response at the end of Cycle 6
CR/PR (unconfirmed)	SD	SD
SD	CR/PR (unconfirmed)	SD
SD	SD	CR/PR (unconfirmed)

Overall response rate (ORR)

The ORR is defined as the proportion of patients with a best response of CR or partial response. The number and percentage of patients achieving an ORR will be summarized by cohort and combination partner (Exemestane or Fulvestrant) within each cohort. The estimate of the ORR will be presented with a 2-sided 95% exact binomial confidence interval. The ORR will be determined based on both unconfirmed and confirmed best overall response (see Section 7.8.3 Additional Efficacy Endpoints for definitions) for the response-evaluable population.

Progression-free survival (PFS)

Progression-free survival is defined as the time from the date of first MLN0128 administration to the date of first documentation of disease 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:
(earliest date of progression or death – date of first dose of MLN0128+ 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 in Table 7.a.

Table 7.a Handling of Missing Response Assessment and Censoring

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 Assessment: investigator response assessment other than Unable to Assess, unknown or missing (i.e. CR, PR, SD or PD).		

PFS Analysis

The Kaplan-Meier method will be used to analyze the distribution of PFS for the Safety Population. 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, 12 and 18 and 24 months will be presented.

The source of PFS (death or progressive disease) and the status of subjects who are censored in the PFS Kaplan-Meier analysis [no post baseline tumor assessment and no death, on-study (on treatment, in follow-up), Lost to follow-up, and received subsequent anti-cancer therapy] will be tabulated.

PFS will be summarized by cohort and combination partner (Exemestane or Fulvestrant) within each cohort.

Overall survival (OS)

Overall survival in months is defined as: (date of death – date of first dose of MLN0128 + 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 number and percentage of patients experiencing an event, the number and percentage of patients who are censored, the 25th, 50th (median), and 75th percentiles (and 95% CIs), and Kaplan-Meier estimates at 6 and 12 months (or other appropriate time points) will be presented for each cohort and combination partner.

OS will be summarized by cohort and combination partner (Exemestane or Fulvestrant) within each cohort.

Change in tumor size from baseline

Waterfall plots of the best percent of change from baseline in the sum of the longest diameter (SLD) of the target lesions will be generated for each cohort (legend for combination partner).

7.8.3 Additional Efficacy Endpoint(s)

Best Overall Response

Best Overall Response (unconfirmed): The best response after the first dose of study drug until subsequent therapy ordered from best to worst: Complete Response, Partial Response, Stable Disease, Progressive Disease. The best response can also be Unable to Assess, Unknown, or No assessment performed if this is the only investigator assessment of objective response available for the patient.

Best Overall Response (confirmed): The best response after the first dose of study drug until subsequent therapy ordered from best to worst: Complete Response, Partial Response, Stable Disease, Progressive Disease. The best response can also be Unable to Assess, Unknown, or No assessment performed if this is the only investigator assessment of objective response available for the patient.

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.

Confirmation Derivation Rules		
Overall response 1st time point	Overall response subsequent time point	BEST overall response
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 minimum criteria for SD is needed as the first protocol scan is at the end of cycle 2, approximately 8 weeks from first dose.

The number and percentage of patients in each response category (CR, PR, SD, SD-16, SD-24, Progressive Disease, Unable to Assess, Unknown, or no post baseline response assessment) will be summarized by cohort and combination partner (Exemestane or Fulvestrant) within each cohort.

Duration of Response (DOR)

The duration of objective response will be calculated for those patients with a best response of CR or PR, 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 response assessment if there is no progressive disease. For phase 2 the Kaplan-Meier method will be used to analyze the DOR. 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 will be presented.

Duration of Stable Disease

The duration of stable disease will be calculated for those patients with a best response of SD. The duration of SD is the number of days from cycle 1 day 1 until progressive disease or until the last response assessment if there is no progressive disease (listing).

7.8.4 Exploratory Efficacy Endpoints

CCI

CCI

[redacted]

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The PK of MLN0128 on Cycle 1 Day 15 and Cycle 2 Day 1 obtained during the phase 1b (Parts 1 and 2) will be assessed based on evaluable patients. The MLN0128 plasma concentrations collected during the phase 2 will be included in data listings in the clinical study report.

The exemestane plasma concentrations obtained in the phase 1b (Parts 1 and 2) will be presented in data listings in the clinical study report; however, no exemestane PK parameters will be estimated and/or reported, due to the limited amount of PK evaluable data.

For the purposes of assessing a potential DDI between MLN0128 and exemestane on MLN0128, plasma concentration-time data and relevant PK parameters (such as C_{max}, AUC_{24h}, and $t_{1/2}$) of MLN0128 will be compared against historical single-agent PK data. The results of this PK evaluation will not be part of the clinical study report.

In addition, PK data generated during the phase 1b and phase 2 in this study may be combined with data from other studies in which the PK of MLN0128 is characterized for population PK analysis. The results of population PK analysis will be presented in a separate report. This will include the sparse PK data collected during the phase 2 portion of the study.

PK data from the phase 1b portion of the study will be summarized as described below.

Pharmacokinetic Concentrations

Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, geometric coefficient of variation, median,

minimum, and maximum) will be used to summarize the MLN0128 plasma concentrations. For the estimation of mean concentration in plots and tabular summaries, BLQ values will always be replaced by zero.

Linear and semi-logarithmic plots of the mean (+SD) MLN0128 plasma concentrations versus scheduled sampling times will be provided for each intense sampling study visit (Cycle 1 Day 15 and Cycle 2 Day 1) segregated by treatment group, as follows:

1. MLN0128 5 mg QD [unmilled API, light meal] + Exemestane.
2. MLN0128 5 mg QD [unmilled API, light meal] + Fulvestrant.
3. MLN0128 3 mg QD [milled API, empty stomach] + Exemestane.
4. MLN0128 3 mg QD [milled API, empty stomach] + Fulvestrant.
5. MLN0128 4 mg QD [milled API, empty stomach] + Exemestane.

Linear and semi-logarithmic plots of individual MLN0128 plasma concentrations versus actual sampling time will be provided for each treatment group and segregated by study visit (Cycle 1 Day 15 and Cycle 2 Day 1) eg, for MLN0128 the Cycle 1 Day15 and Cycle 2 Day 1 will be overlayed on the same plot.

In all Cycle 1 Day 15 MLN0128 plasma concentration versus time plots, pre-dose concentrations will be duplicated and the replicate value will then be imputed as the 24-hour post-dose concentration, thereby extending the PK profile from 8 hours to 24 hours.

All individual patient plasma MLN0128 and exemestane concentration data will be presented in a data listing. MLN0128 imputed 24-hour concentration values will be flagged in listings and will be accompanied by an appropriate footnote.

Pharmacokinetic Parameters

PK parameters will be estimated using non-compartmental methods with WinNonlin® Professional Version 7.0 or higher (Certara USA, Inc., Princeton, NJ). The plasma PK parameters will be estimated from the concentration-time profiles for all PK population patients. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If an actual time is missing the nominal time may be used.

In addition, for the estimation of the Cycle 1 Day 15 MLN0128 plasma PK parameters, pre-dose concentrations will be duplicated and the replicate value will then be imputed as the 24-hour post-dose concentration, thereby extending the PK profile from 0 to 8 hours to 0 to 24 hours. Hence, all Cycle 1 Day 15 PK parameters will be derived over a period of 24 hours.

All individual patient PK parameter data will be in a data listing. Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation,

median, minimum value, and maximum value) will be used to summarize the calculated PK parameters. Additionally, geometric mean and geometric coefficient of variation will be calculated for concentration parameters (such as C_{max} and C_{trough}) and AUC parameters (such as AUCt and AUC_{24h}), clearance parameters (CL/F), and volume parameters (V_z/F). For T_{max}, only median, minimum value, and maximum value will be presented.

Descriptive statistics reported in the main body of the CSR will include sample size, geometric mean and geometric coefficient of variation for concentration, AUC, clearance and volume parameters; arithmetic mean, coefficient of variation, and sample size will be reported for λ_z and t1/2; and median and range for T_{max}.

Data permitting, the following steady-state PK parameters will be calculated for MLN0128 following Cycle 1 Day 15 by noncompartmental analysis:

- Observed maximum plasma concentration (C_{max}).
- Time to observed maximum plasma concentration (T_{max}).
- Area under the plasma concentration-time curve from time 0 to time of last measurable concentration (AUCt).
- Area under the plasma concentration versus time curve from zero to 24 hours (AUC_{24h}).
- Area under the plasma concentration-time curve from time 0 to 4 hr (AUC_{4h}).
- Area under the plasma concentration-time curve from time 0 to 8 hr (AUC_{8h}).
- End of dosing interval (trough) concentration (C_{trough}).
- Terminal disposition half-life (t1/2).
- Apparent oral clearance (CL/F).
- Apparent terminal phase volume of distribution (Vz/F).

The following Cycle 1 Day 15 PK parameters will also be reported in a separate listing of supplementary PK parameters:

- Terminal phase number of data points (Number).
- Upper time for calculation of terminal elimination rate constant (λ_z upper).
- Lower time for calculation of terminal elimination rate constant (λ_z lower).
- Terminal disposition phase rate constant (λ_z).
- Terminal phase regression adjusted R^2 (R^2_{adj}).

Data permitting, the following steady-state PK parameters will be calculated for MLN0128 following Cycle 2 Day 1 by noncompartmental analysis:

- $C_{max.}$
- $T_{max.}$

- AUCt.
- AUC_{4h}.

Descriptive statistics will be presented for the MLN0128 plasma PK parameters on Cycle 1, Day 15 and Cycle 2, Day 1 for the following groups:

1. MLN0128 5 mg QD [unmilled API, light meal] + Exemestane.
2. MLN0128 5 mg QD [unmilled API, light meal] + Fulvestrant.
3. MLN0128 3 mg QD [milled API, empty stomach] + Exemestane.
4. MLN0128 3 mg QD [milled API, empty stomach] + Fulvestrant.
5. MLN0128 4 mg QD [milled API, empty stomach] + Exemestane.

Dot plots of selected PK parameters vs treatment group will be generated for Cycle 1 Day 15 (Cmax, AUC4h, AUC8h and AUC24h) and Cycle 2 Day 1 (Cmax, AUC4h).

7.9.2 Pharmacodynamic Analysis

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[redacted]

7.10 Other Outcomes

CCI

[redacted]

CCI

[redacted]

7.11 Safety Analysis

7.11.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or later (based on version at time of database lock). Treatment-emergent AEs are defined as: AEs that occur after the first dose of MLN0128 and within 30 days after the last dose of MLN0128.

Treatment-emergent AEs will be tabulated by MedDRA system organ class and preferred term and will include the following categories

- 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 TEAEs.
- Serious drug-related TEAEs.
- The most commonly reported treatment-emergent AEs by preferred term (at least 10% of patients).
- Most frequent non-serious TEAEs (>5% of patients in both cohorts sorted by preferred term).

Patients reporting the same event more than once will have that event counted only once within each system organ class, 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 pigmentation
	Mucosal inflammation	Mucosal roughness
	Mucosal membrane hyperplasia	Mucosal toxicity
	Mucosal necrosis	Mucosal ulceration
	Mucosal pain	Mucous membrane disorder
	Oedema mucosal	Leukoplakia
	Mucosal infection	Drug eruption
	Mucosal excoriation	Fixed eruption
	Erythroplasia	Mucocutaneous haemorrhage
	Burning sensation mucosal	
	Paraesthesia mucosal	
Rash	Mucocutaneous rash	Rash papular
	Nodular rash	Rash rubelliform
	Rash	Rash scarlatiniform
	Rash erythematous	Rash vesicular
	Rash generalised	Rash maculovesicular
	Rash macular	Rash morbilliform
	Rash maculo-papular	

For the phase 1 portion a by-subject listing of DLTs in Cycle 1 will be generated.

The number and percentage of subjects experiencing treatment emergent AEs resulting in discontinuation of study drug (action on study drug=DISCONTINUED FROM STUDY) will be summarized by MedDRA system organ class, and preferred term.

A by-subject listing of treatment-emergent AEs resulting in discontinuation of study drug and treatment-emergent AEs resulting in dose modifications (held or reduced) will be generated.

A by-subject listing of the deaths will be presented. An on-study death is defined as a death that occurs between the first dose of study drug and within 30 days of the last dose of study drug.

7.11.2 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 from baseline to the worst post 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, Calcium - decreased, Calcium – increased, Glucose – decreased, Glucose – increased, Potassium – decreased, potassium – increased, magnesium – decreased, magnesium – increased, sodium – decreased, sodium – increased, triglycerides – increased, albumin –decreased, phosphaste – decreased, amylase – increased.

For phase 2 the actual values and change from baseline in clinical laboratory parameters (in SI units) will be summarized 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 6 cycles. Figures of mean actual values at each scheduled visit up to 6 cycles will also be generated for these clinical laboratory parameters (in SI units).

7.11.3 Vital Signs

For phase 1 descriptive statistics for vital sign results (diastolic and systolic blood pressure, heart rate and body weight) will be summarized as follows:

- Baseline value (C1D1 or screening if C1D1 is not available).
- Minimum post-baseline value.
- Change to Minimum post-baseline value.
- Maximum post-baseline value.
- Change to Maximum post-baseline value.

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

In addition to the above for phase 2 the actual values and change from baseline will be summarized over time for each cohort up to 6 cycles.

7.11.4 12-Lead ECGs

For phase 1 descriptive statistics for ECG parameters (ventricular rate, PR, QRS, QT, and QTc (Fridericia) will be summarized as follows:

- Baseline value (C1D1 or screening if C1D1 is not available).
- Minimum post-baseline value.
- Change to Minimum post-baseline value.
- Maximum post-baseline value.
- Change to Maximum post-baseline value.

The number and percent of subjects with increases >30 ms and >60 ms from pre-dose in QTcF will be summarized.

In addition, for phase 2 the actual values and change from baseline will be summarized over time for each cohort up to 6 cycles (including 2H and 4H post-dose values at Cycle 1 Day 1 and Cycle 1 Day 15 visits). 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 = 60 seconds/ventricular rate in beats/minute]

7.11.5 Other Observations Related to Safety

Not Applicable

7.12 Interim Analysis

There will be 3 interim analyses for futility in the Everolimus-Resistant Cohort and 2 interim analyses for futility in the Everolimus-Sensitive Cohort. The investigator-assessed CBR-16 rate will be used as the endpoint for the interim analysis. The interim analysis will be based on response-evaluable patients who have had the opportunity to complete a minimum of 4 cycles of treatment with MLN0128 or have discontinued treatment with MLN0128 before the end of Cycle 4.

In the Everolimus-Resistant Cohort, there will be 3 interim analyses based on the following assumptions:

- Ineffective CBR-16 rate (Ho): 10%.

- Effective CBR-16 rate (Ha): 20%.
- Alpha = 10%; power = 80%.
- Prior Beta Distribution Parameters: ao = 0.10, b0 = 0.90.
- Probability of early termination under Ho: 68%.

Timing of Interim Analyses in the Everolimus-Resistant Cohort

Stage	No. of Patients Evaluated	Number of Patients With CBR-16 to Proceed or Declare Active
1	29	≥3
2	39	≥4
3	49	≥6
Final	56	≥9

Abbreviations: CBR-16 = defined as the proportion of patients who achieve complete response or partial response of any duration, or stable disease) ≥ 16 weeks; No. = number.

In the Everolimus-Sensitive Cohort, there will be 2 interim analyses based on the following assumptions:

- Ineffective CBR-16 rate (Ho): 15%.
- Effective CBR-16 rate (Ha): 30%.
- Alpha = 5%; power = 80%.
- Prior Beta Distribution Parameters: ao = 0.15, b0 = 0.85.
- Probability of early termination under Ho: 71%.

Timing of Interim Analyses in the Everolimus-Sensitive Cohort

Stage	No. of Patients Evaluated	Number of Patients With CBR-16 to Proceed or Declare Active
1	23	≥4
2	38	≥7
Final	48	≥12

Abbreviations: CBR-16 = defined as the proportion of patients who achieve complete response or partial response of any duration, or stable disease) ≥ 16 weeks; No. = number.

7.13 Changes in the Statistical Analysis Plan

The exemestane concentrations will not be summarized and exemestane PK parameters will not be estimated and/or reported due to the limited amount of PK evaluable data.

8.0 REFERENCES

1. Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clin Trials 2008;5(2):93-106.

9.0 DATA LISTINGS

The below subject-level listings will be generated:

- Disposition (date of first dose, date of last dose, number of cycles, reason for discontinuation of study treatment).
- Populations (can be included with disposition listing).
- Demographics.
- Baseline characteristics.
- Prior therapy.
- Study drug exposure.
- TEAEs leading to study drug discontinuation.
- TEAEs resulting in dose modifications.
- Serious AEs.
- On-study deaths.
- DLTs during Cycle 1 (Phase 1b).
- Pharmacokinetic concentrations (including sampling times) for MLN0128 and Exemestane.
- Pharmacokinetic parameters for MLN0128.
- CCI [redacted]
- CCI [redacted]
- Efficacy (target lesions, non-target lesions, investigator assessment of response, best response (confirmed and unconfirmed), duration of response, duration of stable disease).

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	25-Jul-2018 19:29 UTC
	Clinical Science Approval	25-Jul-2018 19:46 UTC
	Clinical Pharmacology Approval	26-Jul-2018 01:09 UTC
	Biostatistics Approval	26-Jul-2018 14:21 UTC