Title: An Open-Label Phase 2 Study of MLN0128 (A TORC1/2 Inhibitor) in Combination With Fulvestrant in Women With ER-Positive/HER2-Negative Advanced or Metastatic Breast Cancer That Has Progressed During or After Aromatase Inhibitor Therapy

MLN0128 in Combination With Fulvestrant in Women With Advanced or Metastatic Breast Cancer After Aromatase Inhibitor Therapy

NCT Number: NCT02756364

SAP Approve Date: 04 December 2018

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C31006

An Open-Label Phase 2 Study of MLN0128 (A TORC1/2 Inhibitor) in Combination With Fulvestrant in Women With ER-Positive/HER2-Negative Advanced or Metastatic Breast Cancer That Has Progressed During or After Aromatase Inhibitor Therapy

PHASE 2

Version: Final

Date: 04 December 2018

Prepared by:

PPD

Based on:

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Protocol Date: 02 October 2017

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2.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CBR	clinical benefit rate
CR	complete response
CDK	cyclin-dependent kinase
CT	computed tomography
ctDNA	circulating tumor DNA
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
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
EORTC QLQ-BR23	European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire
ER	estrogen receptor
HbA1c	glycosylated hemoglobin, hemoglobin A1c
HER2	human epidermal growth factor receptor-2
HR	hazard ratio
IV	intravenous; intravenously
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MLN0128	also known as TAK-228
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
PP	per protocol
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PTEN	phosphatase and tensin homolog
QD	quaque die; each day; once daily
QOL	quality of life
QW	every week
QTc	rate-corrected QT interval (msec)

RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
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
WHO	World Health Organization

3.0 OBJECTIVES

3.1 Primary Objectives

The primary objectives are:

- To compare the PFS of patients treated with the combination of fulvestrant+daily MLN0128 versus patients treated with single-agent fulvestrant.
- To compare the PFS of patients treated with the combination of fulvestrant+weekly MLN0128 versus patients treated with single-agent fulvestrant.

3.2 Secondary Objectives

The secondary objectives are:

- To compare secondary efficacy endpoints in patients treated with the combination of fulvestrant+daily MLN0128 versus patients treated with single-agent fulvestrant.
- To compare secondary efficacy endpoints in patients treated with the combination of fulvestrant+weekly MLN0128 versus patients treated with single-agent fulvestrant.
- To assess the safety and tolerability of the combination of fulvestrant+MLN0128.
- To collect plasma concentration-time data with sparse PK sampling (combination fulvestrant+MLN0128 treatment arms [Arm B and Arm C] only), to contribute to future population PK analysis.

3.3 Additional Objectives

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

To assess the HRQL and symptoms, as measured by the European Organization for Research and Treatment of Cancer QLQ Questionnaire, version 3.0 (EORTC QLQ-C30) and the EORTC QLQ Breast Cancer-Specific Questionnaire (EORTC QLQ-BR23), among the 3 treatment arms.

3.4 Exploratory Objectives

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3.5 Study Design

3.5.1 Enrollment and Randomization

This is an open-label, randomized, 3-arm, multicenter, phase 2 study of the efficacy and safety of the combination of fulvestrant+daily MLN0128 compared with single-agent fulvestrant, and the combination of fulvestrant+weekly MLN0128 compared with single-agent fulvestrant, in the treatment of postmenopausal women with advanced or metastatic ER-positive/HER2-negative breast cancer that has progressed during or after AI therapy. Patients who provide written informed consent and meet all eligibility criteria will be randomized 1:1:1 to 1 of 3 treatment arms via the interactive response technology (IRT):

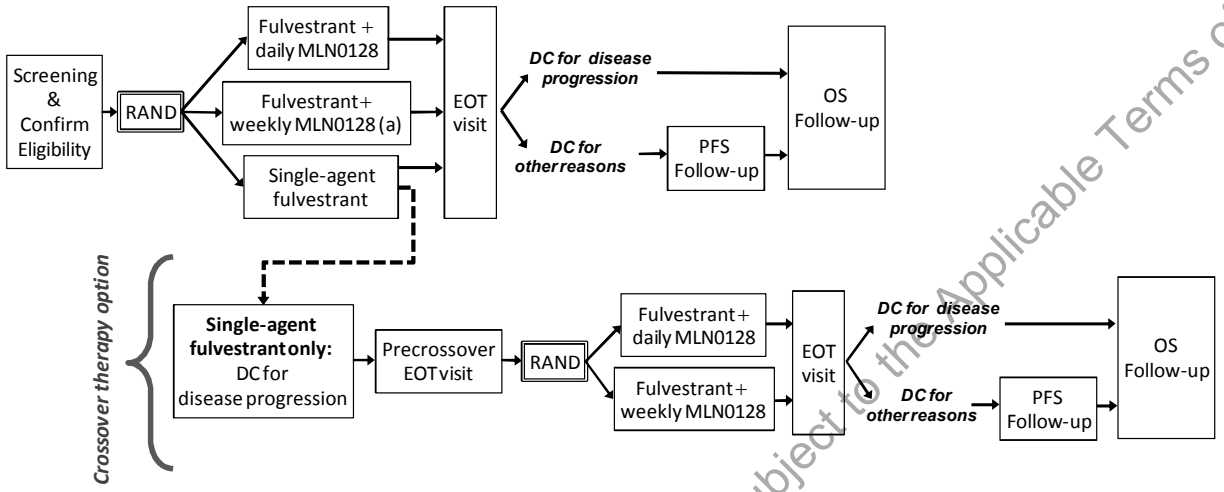
- Arm A, single-agent fulvestrant: fulvestrant, 500 mg intramuscularly (IM), on Cycle 1 Days 1 and 15 (loading regimen), and then on Day 1 of each subsequent 28-day cycle.
- Arm B, combination of fulvestrant+daily MLN0128: fulvestrant as above and MLN0128, 4 mg PO QD continuously.
- Arm C, combination of fulvestrant+weekly MLN0128: fulvestrant as above and MLN0128, 30 mg PO QW continuously.

Patients will be stratified at randomization according to the presence or absence of visceral metastasis, previous sensitivity to hormonal therapy, and previous exposure to CDK 4/6 inhibitors. Visceral metastasis is defined as all lesions not included in the following list: breast, skin, subcutaneous tissue, lymph node or bone. Previous sensitivity to hormonal therapy is defined as at least 24 months of endocrine therapy before recurrence in the adjuvant setting (ie, in patients who have not received previous endocrine therapy in the metastatic setting) or a response or stabilization for at least 24 weeks of the most recent endocrine therapy for advanced/metastatic disease.

Enrollment will be managed via the IRT to ensure that approximately 40% of enrolled patients have previously received a CDK4/6 inhibitor in combination with an AI. Enrollment of non-CDK4/6 pretreated patients may be stopped in the case that 60% or greater of enrollment has occurred with only non-CDK4/6 pretreated patients.

Enrollment is defined as being randomized to a treatment arm. The first dose of study drug must be administered within 5 days after randomization on study. Patients will receive study medication(s) in 28-day cycles. The study design is displayed in Figure 3.a.

Figure 3.a C31006 Study Design



DC=discontinuation, EOT=End-of-Treatment, OS=overall survival, PFS=progression-free survival, RAND=randomization.
(a) The weekly dose of 30 mg MLN0128 will be tested in a safety lead-in of 6 patients in this study (as detailed in Section 3.5.2) to ensure safety and tolerability of the combination with fulvestrant.

3.5.2 Weekly MLN0128 Dose Confirmation (Arm C)

This will be the first study in which weekly MLN0128 will be combined with fulvestrant. Therefore, a safety and tolerability assessment will be performed for patients treated with fulvestrant+weekly MLN0128 (30 mg) after the first 6 DLT-evaluable patients have completed 1 cycle (ie, Cycle 1 Day 28). Patients will be considered evaluable for DLT assessment if they have completed all scheduled study visits during the first cycle and have received at least 3 (75%) of the 4 planned doses of MLN0128 in combination with fulvestrant in Cycle 1. The 30 mg starting dose for weekly MLN0128 will be confirmed or adjusted based on the DLTs observed:

- If ≤1 DLT occurs, the MLN0128 dose for this treatment arm will remain the same (ie, 30 mg weekly MLN0128, in combination with fulvestrant).
- If ≥2 DLTs occur, all patients subsequently randomized to this treatment arm will receive a starting dose of 20 mg weekly MLN0128, in combination with fulvestrant. The starting dose reduction will be documented in formal written communication to all study sites.

DLTs will be assessed and collected in the database for the first 6 evaluable patients in Arm C only (fulvestrant+weekly MLN0128). DLTs are not applicable to patients in Arm A or Arm B at any time in the study, or to patients in Arm C who are not included in the safety and tolerability assessment, or to cross-over patients. Enrollment of patients into the study will continue while this safety and tolerability assessment is conducted. For any patients initially assigned to the

30 mg QW starting dose, the MLN0128 dose may be decreased if necessary per the dose modification criteria outlined in the protocol.

3.5.3 Study Evaluations

Safety assessments (including AEs, SAEs, laboratory assessments, vital signs, electrocardiograms (ECGs), Eastern Cooperative Oncology Group [ECOG] performance status, and weight) will be performed throughout the treatment period, including the End-of-Treatment (EOT) Visit, to evaluate the safety and tolerability of MLN0128. 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.

HRQL will be assessed via the EORTC QLQ-C30 and EORTC QLQ-BR23 instruments throughout the treatment period, including the EOT Visit.

Radiological tumor evaluations (computed tomography [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 RECIST guidelines (Version 1.1). Radiographic tumor evaluations will be performed by the investigator at the time points specified in the Schedule of Events.

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Blood samples will be collected (from patients in the combination fulvestrant+MLN0128 treatment arms [Arm B and Arm C] only) to contribute data to an overall population plasma PK analysis, in combination with data from the other clinical studies of MLN0128.

Patients will receive study medication(s) until PD, unacceptable toxicity, or withdrawal of consent. Patients who discontinue study medication will complete an EOT Visit 30 to 40 days after the last dose of study drug. The EOT Visit should be conducted before the initiation of subsequent anticancer therapy, even if it occurs sooner than 30 days after the last dose of study drug. Patients who discontinue study treatment for reasons other than PD will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the EOT Visit and then every 3 months (±1 week), until PD or start of another anticancer therapy, whichever occurs first. After PD or start of another anticancer therapy, patients will be followed for survival every 6 months (±1 week).

3.5.4 Potential for Crossover Treatment

Patients in the single-agent fulvestrant arm (Arm A) who have radiographically confirmed PD may be allowed to receive crossover treatment with the combination of fulvestrant+MLN0128).

Once documented PD 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 exclusion for prior fulvestrant therapy would not apply), and eligibility for crossover will be confirmed by the sponsor's project clinician (or designee). Eligible patients will then be randomized via the IRT in a 1:1 ratio to either fulvestrant+daily MLN0128 or fulvestrant+weekly MLN0128.

It is recommended that crossover treatment begin within 28 days (+10 days) after documented disease progression (imaging date of PD), with the goal of maintaining the ongoing schedule of fulvestrant therapy (ie, dosing every 28 days). Whenever possible, MLN0128 should be initiated at the next scheduled dose of fulvestrant but only when the patient has completed the precrossover screening requirements and is eligible to continue. If the crossover treatment cannot begin within 28 days (+10 days) after documented PD, contact the medical monitor.

Patients may receive crossover treatment until they experience PD 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 fulvestrant 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 (as detailed in the Schedule of Events) and presented separately.

3.5.5 Potential for Single-Agent MLN0128 Dosing

If fulvestrant is discontinued for a patient in either combination arm (Arm B or Arm C), the patient may continue receiving MLN0128 at their current dose if, after discussion between the investigator and sponsor, it is determined that the patient would derive benefit from continued treatment with single-agent MLN0128 and there are no safety concerns.

4.0 ANALYSIS ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is:

- PFS.

4.2 Secondary Endpoints

The secondary endpoints are:

- Overall survival (OS).
- TTP.
- Objective response rate (ORR); defined as CR+PR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- CBR; defined as CR+PR+SD with SD of any duration, and CBR with SD duration of at least 6 months.
- The number and percentage of patients with TEAEs.

4.3 Health-Related Quality of Life Endpoints

The HRQL endpoints are:

- Changes from Baseline in functional and symptom scores, and global health status and quality of life score from the EORTC QLQ-C30 questionnaire.
- Changes from Baseline in functional and symptom scales from the EORTC QLQ-BR23 questionnaire.

4.4 Exploratory Endpoints

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5.0 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint is PFS. Assuming that the median PFS is 4 months for fulvestrant [1] and that the combination of fulvestrant and MLN0128 (administered either QD or QW) can improve the median PFS to 8 months (HR of 0.5), then a total of 72 PFS events are needed for each pair-wise comparison. Each treatment arm will require 51 patients. The calculations are based on a power of 90%, 2-sided alpha of 10%, and a dropout rate of 10% due to either lost to follow-up or withdrawal of consent.

The accrual duration will be approximately 14 months. The final analysis for the pair-wise comparisons of PFS between fulvestrant+MLN0128 QD and fulvestrant, and between fulvestrant+MLN0128 QW and fulvestrant, is estimated to occur approximately 20 months after the first patient is randomized.

6.0 METHODS OF ANALYSIS AND PRESENTATION

6.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.3.

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.

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: fulvestrant vs. fulvestrant + MLN0128 QD and fulvestrant vs. fulvestrant + MLN0128 QW.

6.1.1 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 6.10. Data imputation rules for incomplete dates are described in Appendix B.

6.1.2 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.

6.1.3 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 purposes 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.

6.2 Analysis Sets

- Full analysis set: all randomized patients. Patients will be analyzed according to the randomization assignment. The ITT population 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 population will be used for all safety analyses. In addition, the safety population will be used for a sensitivity analysis of secondary efficacy endpoints ORR, CBR, CBR with SD duration at least 6 months 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 or bone lesions (lytic or mixed [lytic plus sclerotic]) in the absence of measurable disease at Baseline, and have 1 post-Baseline disease assessment. Patients will be analyzed according to the randomization assignment. The response-evaluable population will be used for the primary analysis of secondary efficacy endpoints of ORR, CBR, CBR with SD duration at least 6 months and the best overall response.

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

6.3 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 database lock), discontinued from the study, and primary reason to discontinue from the study. 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 fulvestrant arm who crossed over to receive fulvestrant + MLN0128 QD or fulvestrant + MLN0128 QW will be summarized.

6.4 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.
  - Adults (18-64 years).
  - From 65 to 84 years.
  - 85 years and over.
- Height (cm).
- Weight (kg) – screening if available otherwise C1D1.
- Ethnicity.
- Race.
- Country/Site (Spain, United States, Canada).

Baseline characteristics consist of:

- Time since first diagnosis (years) [(date of first dose – date of initial diagnosis)/365.25)].
- Time since diagnosis of M1 or locoregional recurrence (years).
- Sites of metastatic disease (visceral, bone-only, other).
- Number of metastatic sites (1, 2, ≥3).
- ECOG Performance Status.

Stratification factors consist of:

- Presence or absence of visceral metastasis.
- Previous sensitivity to hormonal therapy.
- Previous exposure to cyclin-dependent kinase (CDK) 4/6 inhibitors.

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

6.5 Medical History and Concurrent Medical Conditions

Medical history will be summarized by MedDRA System Organ Class and preferred term (full analysis set).

6.6 Medication History and Concomitant Medications

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

6.6.1 Prior Therapies

The following will be summarized for the full analysis set:

- Prior lines of chemotherapy (none, 1, 2)
- Number of prior endocrine therapies (1, 2, >3)
- Prior (neo)adjuvant chemotherapy
- Prior metastatic chemotherapy

The number and percent of patients receiving prior therapies in each category and the prior therapies (WHO drug standardized medication name) within each category will be summarized (full analysis set):

- previous chemotherapy
- previous hormonal therapy
- previous targeted therapy

6.6.2 Follow-up Anti-Cancer Therapy

The number and percentage of patients receiving any anti-cancer therapy, and type of anti-cancer therapy will be summarized based on the full analysis set.

6.7 Study Drug Exposure and Compliance

Summaries and descriptive statistics of duration of treatment in weeks [(date of last dose – date of first dose + 1)/7], total number of cycles administered, average daily dose for MLN0128 QD, cumulative dose for each study drug, planned cumulative dose for each study drug and relative dose intensity will be summarized 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.

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

Relative dose intensity = (cumulative dose / planned dose) * 100.

Fulvestrant (500 mg intramuscularly on Cycle 1 Days 1 and 15 (loading regimen), and then on Day 1 of each subsequent 28-day cycle):

- Planned dose (adjusted for delays in the start of a cycle):

  [(number of cycles*500 mg/cycle + 500 mg (C1D15 loading dose)] * [(number of cycles *28 days/cycle) / (date of first dose in last cycle + 28 days – date of first dose)]

MLN0128 4 mg QD:

- Average daily dose (mg/day): Cumulative dose / duration of treatment in days.
- Planned dose: (Date of first dose in last cycle + 28 days – date of first dose) * 4 mg/day.

MLN0128 30 mg QW:

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

Action on Study Drug

The reason for dose modification (omission, delay, reduction) of each study drug will be summarized by cycle (Cycles 1-8), greater than 8 cycles and overall based on the safety analysis set.

6.8 Efficacy Analysis

The analysis of PFS, OS and TTP will be based on the full analysis set. The analysis of ORR, CBR and CBR with SD duration at least 6 months 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.

6.8.1 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

The date of progression is defined as the earliest date of progression or new lesions among target lesions, non-target and new lesion 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/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 of CR, PR, SD or PD (excluding inevaluable or missing assessments)		

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 3, 6, 9, and 12 months will be presented. The primary hypothesis is to be tested at the 0.10 significance level (2-sided). The p-values from a stratified log-rank test and hazard ratios (HR) (and 95% CI) estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates will be presented for the pairwise comparison of fulvestrant to fulvestrant + MLN0128 QD and fulvestrant to fulvestrant + MLN0128 QW. 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.

6.8.1.1 Sensitivity Analyses of the Primary Efficacy Endpoint (PFS)

Sensitivity analyses will be performed to explore the robustness of the results of the primary analysis.

PFS Sensitivity Analysis 1: discrepancy between original stratification in IRT system and corrected stratification in IRT system

The p-values from a stratified log rank test and the hazard ratio along with its 95% confidence interval will be estimated using a stratified Cox regression model with treatment arm and stratification factors as covariates. PFS will be compared between treatment groups using the corrected IRT strata. This analysis will be performed if at least one stratification variable between the original IRT and the corrected IRT disagrees for at least 10% of the randomized subjects.

PFS Sensitivity Analysis 2: account for missing tumor assessment prior to PFS event (progression or death).

This analysis will be performed only if at least 20% of events of disease progression were documented subsequent to missing 2 or more adequate tumor assessments.

- Subjects who miss 2 or more consecutive adequate scheduled tumor assessments immediately followed by an event of disease progression will be censored on the date of their most-recent adequate tumor assessment prior to the missing/inadequate assessments.
- If 2 or more consecutive missing adequate assessments are immediately followed by an adequate assessment with an overall response assignment of SD, PR, or CR, this will deemed sufficient clinical evidence that progression did not occur during the period of missing data and the missing evaluations will be ignored.

6.8.2 Subgroup Analyses

The focus of the subgroup analyses is to assess the consistency of treatment effects across subgroups for the 2 comparisons: fulvestrant vs. fulvestrant + MLN0128 QD and fulvestrant vs. fulvestrant + MLN0128 QW.

The 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% Cis will be presented by subgroup and treatment arm. Forest plots (including the number of events/number of patients in each arm, hazard ratio (HR) and 95% CI within each subgroup for the 2 treatment comparisons) 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.

- Age (< 65 years, ≥65 years).
- Race (white, non-white) [Not Reported will be excluded].
- Region (North America, Europe).

Stratification factors per IRT (original):

- Presence or absence of visceral metastasis.
- Previous sensitivity to hormonal therapy.
- Previous exposure to CDK 4/6 inhibitors.

6.8.3 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 6 months. The analyses of OS and TTP will be done for the full analysis set. The analyses of ORR, CBR, and CBR with SD duration at least 6 months 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 [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 3, 6, 9, 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 fulvestrant vs. fulvestrant + MLN0128 QD and fulvestrant vs. fulvestrant + MLN0128 QW. 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. 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.

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. 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 (fulvestrant vs. fulvestrant + MLN0128 QD and fulvestrant vs. fulvestrant + MLN0128 QW). 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. A stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors will be used to compare CBR between treatment arms (fulvestrant vs. fulvestrant + MLN0128 QD and fulvestrant vs. fulvestrant + MLN0128 QW). 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 6 months

CBR with SD duration of at least 6 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 6 months (see below). A stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors will be used to compare the CBR with SD duration at least 6 months between treatment arms (fulvestrant vs. fulvestrant + MLN0128 QD and fulvestrant vs. fulvestrant + MLN0128 QW). The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each comparison specified above.

SD with a duration of at least 6 months is defined as the number of patients who achieve CR or PR at any time or have SD at the end of Cycle 2, at the end of Cycle 4, and at the end of Cycle 6. 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 6 months will include cases where at least three post baseline scans have SD and the duration of stable disease is greater than 180 days.

The proportion of patients with the following best response will be summarized by treatment group: CR, PR, SD, SD at least 6 months, overall response (ORR), CBR and CBR with SD duration at least 6 months.

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 3, 6, 9, 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 fulvestrant vs. fulvestrant + MLN0128 QD

and fulvestrant vs. fulvestrant + MLN0128 QW. The original IRT stratification factors will be used in models.

CCI

[redacted]

6.9 Pharmacokinetic/Pharmacodynamic Analysis

6.9.1 Pharmacokinetic Analysis

Sparse PK data for MLN0128 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 is characterized for population PK analysis. The results of the population PK analysis will be presented in a separate report.

CCI

[redacted]

6.9.2 Pharmacodynamic Analysis

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[redacted]

6.10 Patient Reported Outcomes

Patient-reported outcome (PRO) assessments will be collected through 2 different instruments: EORTC QLQ-C30 and QLQ-BR23. 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 QLQ-BR23 questionnaires 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 and time to deterioration analyses. Patients with baseline scores, but with no follow-up scores, are not assessable for change from baseline. For time to deterioration they will be censored at Day 1. Published manuals/guidance for EORTC QLQ-C30 and QLQ-BR23 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.

6.10.1 EORTC QLQ-C30 and EORTC QLQ-BR23 Score

Descriptive statistics including the 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 QLQ-BR23 questionnaires, the global health status/QOL score and summary score from the EORTC QLQ-C30 questionnaire up to 12 cycles. In addition, the mean and mean change from baseline of the EORTC QLQ-C30 subscales, the global health status/QOL score, summary score and the EORTC QLQ-BR23 subscales will also be presented over time by treatment group in figures up to 12 cycles (including 95% CI around mean).

The change from baseline of EORTC QLQ-C30 subscales, global health status/QOL, summary score, QLQ-BR23 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 the appropriate covariance structure will be used based on the unstructured 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 12 cycles for each treatment arm. The mean difference in each score and 95% CIs and p values for the pairwise comparison of fulvestrant to fulvestrant + MLN0128 QD and fulvestrant to fulvestrant + MLN0128 QW will be presented at each time point up to 12 cycles.

6.11 Safety Analysis

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

6.11.1 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) [for disclosure reporting]

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

Adverse event of interest	MedDRA Preferred Term	
	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	Oedema mucosal
	Mucosal inflammation	Mucosal infection
	Mucosal membrane hyperplasia	Mucosal excoriation
	Mucosal necrosis	Erythroplasia
	Mucosal pain	Burning sensation mucosal
	Mucosal pigmentation	Paraesthesia mucosal
	Mucosal roughness	Leukoplakia
	Mucosal toxicity	Drug eruption
	Mucosal ulceration	Fixed eruption
	Mucous membrane disorder	Mucocutaneous haemorrhage
Rash	Mucocutaneous rash, Nodular rash, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash popular, Rash rubelliform, Rash scarlatiniform, Rash vesicular	

6.11.1.1 Deaths

All-cause mortality will be tabulated, which includes death of all causes, and deaths related to breast cancer. On-study deaths (from first dose to 30 days after last dose) will be tabulated including deaths related to breast cancer, deaths due to study treatment, and deaths within 30 and 60 days of first dose.

6.11.2 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 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 fulvestrant and fulvestrant + MLN0128 QD arms, and for the fulvestrant + MLN0128 QW patients enrolled prior to protocol amendment no 3. Similarly, the changes from pre-dose to 2 hours post dose for 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 12 cycles. Figures of mean actual values over time will also be generated for these clinical laboratory parameters (in SI units).

6.11.3 Vital Signs

The actual values and change from baseline 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. In addition, the minimum post-baseline value, change to minimum post-baseline value, maximum post-baseline value, and change to maximum post-baseline value will be summarized.

6.11.4 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. 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. In addition, the minimum post-baseline value, change to minimum post-baseline value, maximum post-baseline value, and change to maximum post-baseline value will be summarized.

6.11.5 Other Observations Related to Safety

For ECOG performance status shifts from baseline to the worst post-baseline on study score will be tabulated by treatment arm.

6.12 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 fulvestrant arm (presented by crossover treatment):

- Best overall response prior to/after crossover
- Duration of treatment (weeks) prior to/after crossover
- Reason for discontinuing fulvestrant/reason for discontinuing crossover treatment

6.13 Interim Analysis

CCI [redacted]

6.14 Changes in the Statistical Analysis Plan

- 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.
- 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 fulvestrant vs. fulvestrant + MLN0128 QD and fulvestrant vs. fulvestrant + MLN0128 QW. The protocol did not explicitly state the model for estimating the HRs.

CCI [redacted]

7.0 REFERENCES

1. Turner NC, Ro J, Andre F, Loi S, Verma S, Iwata H, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. New England Journal of Medicine 2015;373(3):209-19.

8.0 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:

- Disposition of subjects (including crossover treatment, if applicable).
- Demographic and other baseline characteristics.
- Stratification Factors.
- Significant protocol deviations.
- 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.
- RECIST response assessment and best overall response based on investigator assessment – Crossover Patients.

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	Biostatistics Approval	04-Dec-2018 15:43 UTC
	Biostatistics Approval	04-Dec-2018 16:21 UTC
	Clinical Science Approval	05-Dec-2018 21:34 UTC