Title: A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C31004

A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer

PHASE 2

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1.1 APPROVAL SIGNATURES

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

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
CBR	clinical benefit rate
CR	complete response
CRF	case report form
CT	computed tomography
CCI	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-EN24	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer Module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
INR	international normalized ratio
IRC	Independent review committee
ITT	intent-to-treat
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
MLN0128	also known as TAK-228
MRI	magnetic resonance imaging
mTOR	mammalian (or mechanistic) target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphoinositide-3-kinase, catalytic alpha polypeptide
PK	pharmacokinetic(s)
PO	by mouth (oral)
PPI	proton pump inhibitor
PR	partial response
PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog

Abbreviation	Term
PT	prothrombin time
QD	*quaque die*; each day; once daily
QD×3 QW	once daily for 3 days each week
QOL	quality of life
QTc	rate-corrected QT interval (msec)
QTcF	QT interval (msec) with Fridericia correction
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TEAE	treatment-emergent adverse events
TORC1	mammalian (or mechanistic) target of rapamycin complex 1
TORC2	mammalian (or mechanistic) target of rapamycin complex 2
TTP	time to progression
ULN	upper limit of the normal range
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is:

- To determine if MLN0128 in combination with weekly paclitaxel improves progression free survival (PFS) compared to weekly paclitaxel alone.

4.2 Secondary Objectives

The secondary objectives of the study are:

- To determine if single-agent MLN0128 improves PFS compared to weekly paclitaxel alone.
- To determine if MLN0128 + MLN1117 improves PFS compared to weekly paclitaxel alone.
- To assess the safety and tolerability of single-agent MLN0128, MLN0128 in combination with paclitaxel, and MLN0128 + MLN1117.
- To evaluate improvement in efficacy measures (endpoints other than PFS) of MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128 + MLN1117 compared to weekly paclitaxel alone.
- To collect plasma concentration-time data with sparse PK sampling to contribute to future population PK analysis.

4.3 Quality of Life Objectives

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

- To assess the QOL and symptoms in patients treated with MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128 + MLN1117 to weekly paclitaxel alone.

4.4 Exploratory Objectives

The exploratory objectives of the study are:

CCI

[redacted]

4.5 Study Design

4.5.1 Overview of Study Design

This study is a phase 2, open-label, randomized, multicenter, 4-arm study of the safety and efficacy of MLN0128 in combination with paclitaxel, single-agent MLN0128, single-agent paclitaxel, and MLN0128 in combination with MLN1117 in adult women with advanced endometrial cancer. The patient population will consist of women with histologic or cytologic diagnosis of endometrial carcinoma (including endometrioid, serous, mixed adenocarcinoma, clear-cell carcinoma, or carcinosarcoma) that is advanced, recurrent, or persistent, that has relapsed or is refractory to curative therapy or established treatments. Patients must have had 1 prior platinum-based chemotherapeutic regimen, but not more than 2 prior systemic chemotherapy regimens.

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. Study drug will be administered in 28-day treatment cycles.

Approximately 242 patients will be randomized at a ratio of 1:1:1:1 to receive study drug in 1 of 4 treatment arms:

Arm A: paclitaxel 80 mg/m2 weekly on Days 1, 8, and 15 of a 28-day cycle

Arm B: paclitaxel 80 mg/m2 weekly on Days 1, 8, and 15 of a 28-day cycle

+ MLN0128 4 mg on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle

Arm C: MLN0128 30 mg once weekly (QW) on Days 1, 8, 15, and 22 of a 28-day cycle

Arm D: MLN0128 4 mg + MLN1117 200 mg on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle

A centralized randomization will be used with the following stratification factors:

- Histological subtype: endometrioid vs. nonendometrioid.
- Lines(s) of prior chemotherapy: 1 vs. 2.
- Prior taxane therapy (other than weekly): yes vs. no.

In the event that enrollment into a treatment arm(s) is closed, patients will be randomized 1:1 into the remaining treatment arms. Paclitaxel will be administered intravenously (IV) while MLN0128 and MLN1117 will be administered PO throughout the study. Patients in Arm A and Arm B will receive paclitaxel alone or paclitaxel + MLN0128 until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients in Arm B who discontinue paclitaxel prior to disease progression may continue to receive MLN0128 alone until they experience disease progression, unacceptable toxicity, or withdraw consent. In addition, patients will receive MLN0128 (in Arm C) or MLN0128 + MLN1117 (in Arm D) continuously until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients who

discontinue study treatment for reasons other than progressive disease will continue to have PFS follow-up visits every 2 months (± 1 week) for the first 6 months after the end-of-treatment (EOT) visit, then every 3 months (± 1 week) until disease progression, death, or start of another anticancer therapy, whichever occurs first. After disease progression, patients will be followed for OS every 3 months (± 1 week).

Patients will attend the EOT visit 30 to 40 days after receiving their last dose of study drug.

Sparse PK samples will be collected from patients enrolled in Arms B, C, and D for determination of the plasma concentration of MLN0128 and/or MLN1117 during Cycle 1 at prespecified time points as described in the Pharmacokinetic Sample Breakdown table in the study protocol. 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. For correlative biomarker analysis, fresh and archival tumor samples will be obtained during screening, as well as a blood sample for CCI at prespecified time points as described in the Schedule of Events in the study protocol. In addition, fresh tumor samples will be obtained 2 to 4 hours after dosing on Cycle 1 Day 22 from patients in Arms C and D to identify adaptive response mechanisms to treatment of MLN0128 or MLN0128 + MLN1117.

Radiological tumor evaluations (computed tomography [CT] scan with 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). Radiographic tumor evaluations will be performed at the time points specified in the Schedule of Events in the study protocol.

Changes in QOL disease-specific symptoms will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Endometrial Cancer Module (EORTC QLQ-EN24). In addition to assessing selected symptoms, these instruments will measure the effects of disease and treatment on physical, role, emotional, cognitive, and social functioning.

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, and laboratory values, vital signs, and electrocardiograms will be obtained to evaluate the safety and tolerability of MLN0128 in combination with paclitaxel, single-agent MLN0128, and MLN0128 + MLN1117.

There will be 2 interim analyses with early stopping rules for futility in the single-agent MLN0128 arm (Arm C) and MLN0128+MLN1117 arm (Arm D).

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is Progression Free Survival (PFS).

5.2 Secondary Endpoints

The secondary endpoints are:

- The number and percentage of patients with treatment-emergent adverse events (TEAEs).
- Overall survival (OS).
- Time-to-progression (TTP).
- Objective response rate (ORR; defined as complete response [CR]+partial response [PR] per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1).
- Clinical benefit rate (CBR; defined as CR+PR+stable disease (SD)) with SD of any duration.
- CBR at 16 weeks (CBR-16 is defined as the proportion of patients who achieve CR or PR of any duration or have SD with a duration of at least 16 weeks).

5.3 Quality of Life Endpoints

The QOL endpoints are:

- Change from baseline in the EORTC QLQ-C30 global health status (GHS)/QOL score to end of study visit.
- Change from baseline in the EORTC QLQ-C30 functioning score to end of study visit.
- Change from baseline in the EORTC QLQ-C30 symptom score to end of study visit.
- Change from baseline in the EORTC QLQ-EN24 score to the end of study visit.

5.4 Exploratory Endpoints

The exploratory endpoints are:

CCI

[redacted]

Note: Exploratory endpoints will not be reported in the Clinical Study Report and these endpoints are not discussed further in the SAP.

6.0 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint of the study is PFS and the primary comparison is between the paclitaxel and the paclitaxel + MLN0128 4 mg QDx3 treatment arm. Assuming the median PFS is 4 months for paclitaxel and paclitaxel + MLN0128 4 mg QDx3 can improve the median to 6.5 months (hazard ratio of 0.615, approximately 38% reduction in the hazard rate) a total of 134 PFS events and 90 patients per treatment arm are required. The calculations are based on a power of 80%, 2-sided alpha of 5%, and a dropout rate of 15% due to lost to follow-up or withdrawal of consent. Enrollment to the third treatment arm of single-agent MLN0128 30 mg QW and the fourth treatment arm of MLN0128 4 mg QDx3 in combination with 200 mg MLN1117 has been closed. The total sample size for the study will be approximately 242 patients.

The total accrual duration will be approximately 25 months to complete enrollment in the paclitaxel and paclitaxel+MLN0128 4 mg QD×3 treatment arms. The final analysis for the primary comparison of PFS between the paclitaxel treatment arm and the paclitaxel + MLN0128 4 mg QDx3 treatment arm will occur approximately 5 months after the last patient is randomized.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

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

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, 25th and 75th percentiles (where specified), minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data. For summaries of categorical variables percentages are based on the number of subjects with non-missing values unless otherwise specified (e.g. objective response rate, clinical benefit rate, CBR at 16 weeks).

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

All statistical tests and resulting p-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values should be presented to 3 decimal places, with values less than 0.001 presented as <0.001.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate. Percentages will be presented to 1 decimal place.

A month is operationally defined to be 30.4375 days.

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

7.1.1 Methods for Handling Missing Data

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

7.1.2 Definitions of Baseline Values

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

7.1.3 Definition of Study Days

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

7.2 Analysis Sets

- Intent-to-treat (ITT) population: 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 population: 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 and CBR-16 and the best overall response and patients will be analyzed according to the randomization assignment.
- Response-evaluable population: patients who receive at least 1 dose of study drug, have measurable disease at Baseline, and have 1 post-Baseline disease assessment. Patients will be analyzed according to the randomization assignment. The response-evaluable population will be used for the primary analysis of secondary efficacy endpoints of ORR, CBR and CBR-16, and the best overall response.
- Per-protocol population: all ITT patients who meet the following criteria:
  - Had at least one adequate post-randomization tumor assessment.
  - Received treatment as randomized.
  - Did not have any major or important protocol deviations that would potentially impact the interpretation of the efficacy analyses.

    The subset of major/important protocol deviations that would exclude a patient from the per protocol population will be based on a review of the protocol deviations in the clinical trial management system and will be documented prior to database lock. The per-protocol population will be used for a sensitivity analysis of PFS, and secondary efficacy endpoints including OS and TTP.

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

7.3 Disposition of Subjects

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

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

7.4 Demographic and Other Baseline Characteristics

Summaries of demographics, baseline characteristics and stratification factors will be presented for subjects in the ITT population.

The demographic characteristics consist of:

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

  Australia and New Zealand

  North America

  - Canada
  - United States

Europe

- Belgium
- Germany
- Italy
- Netherlands
- Norway
- Spain
- United Kingdom

Baseline characteristics consist of:

- Time since initial diagnosis (months) [date of first dose – date of initial diagnosis/(30.4375))].
- Histological classification [Endometrioid adenocarcinoma, NOS; Serous cystadenocarcinoma, NOS; Mixed cell adenocarcinoma; Clear cell adenocarcinoma, NOS; Carcinosarcoma, NOS; Unknown].
- Histological grade [Well differentiated (G1); Moderately differentiated (G2); Poorly differentiated (G3); Undifferentiated (G4)].
- ER status
- PR status
- Microsatellite stability
- ECOG Performance Status (categorical)

Stratification factors consist of:

- Histological subtype: endometrioid vs. non-endometrioid
- Prior lines of chemotherapy: 1 vs. 2
- Prior taxane therapy: yes vs. no.

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

7.5 Medical History and Concurrent Medical Conditions

No summary for medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

No summary for medication history.

The number and percentage of patients taking concomitant medications will be tabulated by WHO standardized medication name based on safety population. Concomitant medications are

medications ongoing at the time of the first dose of study drug or medications that started after first dose and within 30 days of the last dose of study drug.

7.6.1 Prior Therapies

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

- Type of prior anti-cancer therapy (WHO drug standardized medication name).
- Best response to most recent prior therapy.
- Prior therapy in the adjuvant setting (Y, N).
- First systemic chemotherapy for metastatic disease (Y, N).

7.6.2 Follow-up Anti-cancer Therapy

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

7.7 Study Drug Exposure and Compliance

7.7.1 Study Treatments

Cycles consist of 28 days for all treatment arms. In Treatment Arm A, paclitaxel will be administered weekly on Days 1, 8, 15 of a 28-day cycle. In Treatment Arm B, paclitaxel will be administered weekly on Days 1, 8, 15 of a 28-day cycle + MLN0128 administered on Days 2-4, 9-11, 16-18 and 23-25 of a 28-day cycle. In Treatment Arm C, MLN0128 will be administered once weekly on Days 1, 8, 15, and 22 of a 28-day cycle. In Treatment Arm D, MLN0128 and MLN1117 will be administered together, 3 consecutive days per week (on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle), and should be taken on the same days of each week.

7.7.2 Extent of Exposure

Summaries and descriptive statistics of duration of treatment in weeks ((last dose date – start dose date + 1)/7), total number of cycles administered, cumulative dose for each study drug, planned cumulative dose for each study drug and relative dose intensity will be summarized by treatment arm for patients in the safety population. For patients who discontinued Paclitaxel but stayed on MLN0128, number of treatment cycles will be summarized.

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

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

Relative dose intensity = cumulative dose / planned cumulative dose.

Paclitaxel (weekly on Days 1, 8 and 15 of a 28-day cycle)

Relative dose intensity for Paclitaxel (%) is defined as:

*Cumulative dose (mg) / [Number of planned dose from start dose date to last dose date*80mg/ m^2] * 100*

Number of planned dose = Number of completed 28-day cycle from start dose date to last dose date*3 doses per cycle + Number of doses in the uncompleted cycle

MLN0128 QDx3 (Days 2-4, 9-11, 16-18 and 23-25 of a 28-day cycle)

MLN1117 / MLN0128 (Days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle)

Relative dose intensity (%) presented separately for MLN0128 and MLN1117 is defined as:

*{Cumulative dose (mg) / [Number of planned dose from start dose date to last dose date*Starting dose]} * 100*

Number of planned dose = Number of completed week from start dose date to last dose date*3 doses per week + Number of doses in the uncompleted week

MLN0128 QW (Days 1, 8, 15 and 22 of a 28-day cycle)

Relative dose intensity for MLN0128 (%) is defined as:

*Cumulative dose (mg) / [Number of planned dose from start dose date to last dose date*30mg] * 100*

Number of planned dose = Number of completed 28-day cycle from start dose date to last dose date*4 doses per cycle + Number of doses in the uncompleted cycle

7.7.3 Action on Drug

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

7.8 Efficacy Analysis

The analysis of PFS, OS and TTP will be based on the ITT population and the PP population. The analysis of ORR, CBR and CBR-16 will be based on both safety and response-evaluable analysis populations. The primary analysis for all efficacy endpoints are based on the investigator response assessment per RECIST 1.1 criteria.

7.8.1 Primary Efficacy Endpoint(s)

The primary endpoint is PFS, defined as the time from the date of randomization to the date of first documentation of progression or death due to any cause, whichever occurs first. Progression is based on the investigator response assessment per RECIST 1.1 criteria. PFS in months is defined as:

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

In the event of progression, the date of progression is defined as the earliest date among target lesions, non-target and new lesions dates at that particular visit.

For a patient whose disease has not progressed and is last known to be alive, PFS will be censored at the last response assessment that is SD or better.

The approach for handling of missing response assessments and censoring is presented 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 Assessments

Functionally this corresponds to a response assessment with an investigator's assessment other than not evaluable or missing (i.e. CR, PR, SD or PD).

PFS Analysis

The primary efficacy analysis will be based on the ITT population. The Kaplan-Meier method will be used to analyze the distribution of PFS for each treatment arm. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley, and Kaplan-Meier estimates with 95% CIs at 6, 12 and 18 and 24 months will be presented. The primary hypothesis will be tested at the 0.1 significance level (1-sided). The p-values from a stratified log-rank test and hazard ratios (and 95% CI) estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates will be presented for comparison of paclitaxel to paclitaxel+MLN0128, paclitaxel to MLN0128 and paclitaxel to MLN0128+MLN1117. The stratification factors are the histological subtype (endometrioid vs. non-endometrioid), the lines of prior chemotherapy (1vs. 2) and prior taxane therapy (yes vs. no). The original IRT stratification factors will be used in models.

The source of PFS (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.

7.8.1.1 Sensitivity Analyses of the Primary Efficacy Endpoint (PFS)

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

PFS Sensitivity Analysis 1: 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.

PFS Sensitivity Analysis 2: 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 3: repeat the primary PFS analysis using the per-protocol population

PFS Sensitivity Analysis 4: repeat the primary PFS analysis based on IRC assessment (see section 7.8.3)

7.8.1.2 Subgroup Analyses

The analysis of PFS will be repeated in each of the following subgroups. The focus of the subgroup analyses is to assess the consistency of treatment effects and to present number of patients with events/censored, 25th, median and 75th percentile with HR and 95% CI within each subgroup for the 3 comparisons: paclitaxel vs. paclitaxel+MLN0128, paclitaxel vs. MLN0128 and paclitaxel vs. MLN0128+MLN1117. In addition, number of events/number of patients, HR and 95% CI within each subgroup for the 3 treatment comparisons will be presented as part of the forest plots and individual Kaplan-Meier survival curves for each subgroup will be presented.

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

Stratification factors per IRT (original):

- Histological subtype (endometrioid vs. non-endometrioid).
- Lines of prior chemotherapy (1 vs. 2).
- Prior taxane therapy (yes vs. no).

7.8.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include OS, ORR, TTP, CBR with SD of any duration, and CBR with SD duration of at least 16 weeks. The analyses of OS and TTP will be done for both the ITT and the per-protocol populations. The analyses of ORR, CBR and CBR-16 will be done for both the safety and response-evaluable populations.

In the event of response (i.e. overall response is PR or better), the date used for 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 6, 12 and 18 and 24 months will be presented. A stratified log-rank test and hazard ratios (and 95% CI) estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates will be presented for comparison of paclitaxel to paclitaxel+MLN0128, paclitaxel to MLN0128 and paclitaxel to MLN0128+MLN1117. The stratification factors are the histological subtype (endometrioid vs. non-endometrioid), the lines of prior chemotherapy (1vs. 2) and prior taxane therapy (yes vs. no). The original IRT stratification factors will be used in models.

Best Overall Response

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

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

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

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

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

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

Clinical Benefit Rate (CBR)

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

Clinical Benefit Rate at 16 weeks (CBR-16)

CBR at 16 weeks (CBR-16) is defined as the proportion of patients who achieve CR or PR of any duration or have SD with a duration of at least 16 weeks (see below). CBR-16 will be summarized based on unconfirmed best response and confirmed best response. A stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors will be used to compare CBR-16 between treatment arms (paclitaxel vs. paclitaxel+MLN0128, paclitaxel vs. MLN0128 and paclitaxel vs. MLN0128+MLN1117). The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each comparison specified above.

SD for at least 16 weeks is a subset of SD, only calculated for those patients with a best response of SD. It is defined as SD at the end of Cycle 2 and at the end of Cycle 4 (see below for exceptions).

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 (at the end of Cycle 2 and at the end of Cycle 4).

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

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

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

Time to Tumor Progression (TTP)

TTP in months is defined as the time from the date of randomization to the date of first documentation of progression [(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 6, 12 and 18 and 24 months will be presented. A stratified log-rank test and hazard ratios (and 95% CI) estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates will be presented for comparison of paclitaxel to paclitaxel+MLN0128, paclitaxel to MLN0128 and paclitaxel to MLN0128+MLN1117. The stratification factors are the histological subtype (endometrioid vs. non-endometrioid), the lines of prior chemotherapy (1vs. 2) and prior taxane therapy (yes vs. no). The original IRT stratification factors will be used in models.

7.8.3 Additional Efficacy Endpoint(s)

The duration of objective response (DOR) will be calculated for those patients with a best response of CR or PR (for both unconfirmed and confirmed), and is defined as the number of days from the start date of CR, or PR (whichever response is achieved first) until progressive disease or until the last adequate response assessment if there is no progressive disease. The analysis of duration of response will be descriptive in nature and will be based on response-evaluable population.

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

1. If a target lesion at a visit is “too small to measure”, per the CRF completion guidelines the value of 5 mm should have been entered as the diameter. This would be used to calculate the SLD.
2. If 2 target lesions conjoin into a single lesion (status=”coalesce”), per the CRF completion guidelines the LD of the resulting merged lesion is divided by 2 and reported in the CRF for each of the previous TL and then would be included in the SLD.
3. If a target lesion splits into 2 lesions (status=”split”), the LDs of the fragmented portions are added up and reported in the CRF and would be included in the SLD.
4. Sum of the target lesions (SLD) [in mm] is defined as the sum of the longest diameters of all target lesions at each visit.

5. SLD change from baseline at visit x [in mm] is defined as the absolute change in the SLD from baseline to each visit = "SLD at visit x" – "SLD at baseline". Baseline SLD corresponds to the SLD from the screening visit.
6. Percentage change from baseline in SLD [in %] is defined as "SLD change from baseline at visit x" / "SLD at baseline" * 100.
7. Best percentage change in SLD is defined as the percentage change from baseline in SLD at the visit with the smallest SLD value among all the post screening visits.

All images will be collected and quality controlled by a sponsor-specified central imaging vendor. The independent review committee (IRC) will consist of two independent readers, and an adjudicator. For analysis purposes, if the response assessment at a specific timepoint differs between the 2 readers, the adjudicated response assessment will be used.

The concordance in the assessment of progressive disease between the investigator (INV) and the IRC will be summarized for the ITT population for Arms A (paclitaxel) and B (paclitaxel + MLN0128):

- Agreement on PD status
  - PD by both IRC and investigator
    - IRC and investigator agree on timing
    - IRC earlier than investigator
    - IRC later than investigator
  - No PD by either IRC or Investigator
- Disagreement on PD status
  - PD by Investigator but not by IRC
  - PD by IRC but not by investigator

Sensitivity analyses for time-to-event endpoints (PFS, TTP) based on the ITT population and response endpoints (ORR and CBR both unconfirmed and confirmed) for the safety population will be generated based on results from the IRC for Arms A (paclitaxel) and B (paclitaxel + MLN0128).

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

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

7.9.2 Pharmacodynamic Analysis

Biomarker analyses will be exploratory in nature and will be summarized in a separate report.

7.10 Patient Reported Outcomes

Patient-reported outcome (PRO) assessments will be collected through 2 different instruments: EORTC QLQ-C30 and EORTC QLQ-EN24. The ITT population 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 EORTC QLQ-EN24 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 will be used for scoring and handling missing data. In the case where there is no guidance for handling missing data, missing items will be considered missing, they will not be imputed.

7.10.1 EORTC QLQ-C30 and EORTC QLQ-EN24 Scores

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-EN24 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-EN24 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 and EORTC QLQ-EN24 subscales will be analyzed using linear mixed models, including treatment group, visit, the interaction between treatment group and visit, baseline score (and other covariates i.e. stratification factors as per original IRT) as covariates. Random-intercept only model with appropriate covariance structure will be used based on the following covariance structure in order from unstructured, spatial-power and AR(1). The first covariance structure that has all the parameter estimates converged for all the subscales will be used. The estimated means with 95% CIs will be provided at each time point up to 12 cycles for each treatment arm. The mean differences in each score and 95% CIs and p values for the pairwise comparison of paclitaxel to paclitaxel+MLN0128, paclitaxel to MLN0128 and paclitaxel to MLN0128+MLN1117 will be presented at each time point up to 12 cycles.

7.10.2 Percentage of Patients Experiencing Improvement or Deterioration

The subscale scores based on EORTC QLQ-C30 and EORTC QLQ-EN24 and corresponding minimally important differences (MIDs) are defined as shown in Table 7.2. For EORTC QLQ-

EN24, the MID threshold of 5 is used in the absence of referenced MID, which corresponded to the value found in the literature for the other scales of the EORTC questionnaire.

Table 7.b Definition of Minimally Important Difference (MID) Based on EORTC QLQ-C30 and EORTC QLQ-EN24

Subscale	Individual Items	MID	Deterioration from Baseline
EORTC QLQ-C30			
Functional scales			
Physical functioning	1-5	6	Decrease (CFB ≤ -MID)
Role functioning	6-7	7	Decrease (CFB ≤ -MID)
Emotional functioning	21-24	7	Decrease (CFB ≤ -MID)
Cognitive functioning	20, 25	4	Decrease (CFB ≤ -MID)
Social functioning	26-27	6	Decrease (CFB ≤ -MID)
Global health status			
Quality of life	29-30	5 and 10	Decrease (CFB ≤ -MID)
Symptom scales/items			
Fatigue	10, 12, 18	6	Increase (CFB ≥ MID)
Nausea and vomiting	14-15	4	Increase (CFB ≥ MID)
Pain	9, 19	7	Increase (CFB ≥ MID)
Dyspnoea	8	5	Increase (CFB ≥ MID)
Insomnia	11	5	Increase (CFB ≥ MID)
Appetite loss	13	6	Increase (CFB ≥ MID)
Constipation	16	6	Increase (CFB ≥ MID)
Diarrhoea	17	4	Increase (CFB ≥ MID)
Financial difficulties	28	4	Increase (CFB ≥ MID)
EORTC QLQ-EN24			
Functional scales			
Sexual interest	49	5	Decrease (CFB ≤ -MID)
Sexual activity	50	5	Decrease (CFB ≤ -MID)

Table 7.b Definition of Minimally Important Difference (MID) Based on EORTC QLQ-C30 and EORTC QLQ-EN24

Subscale	Individual Items	MID	Deterioration from Baseline
Sexual enjoyment	54	5	Decrease (CFB ≤ -MID)
Symptom scales			
Lymphoedema	31-32	5	Increase (CFB ≥ MID)
Urological symptoms	34-37	5	Increase (CFB ≥ MID)
Gastrointestinal symptoms	38-42	5	Increase (CFB ≥ MID)
Poor body image	47-48	5	Increase (CFB ≥ MID)
Sexual/vaginal problems	51-53	5	Increase (CFB ≥ MID)
Pain in back and pelvis	33	5	Increase (CFB ≥ MID)
Tingling/numbness	43	5	Increase (CFB ≥ MID)
Muscular pain	44	5	Increase (CFB ≥ MID)
Hair loss	45	5	Increase (CFB ≥ MID)
Taste change	46	5	Increase (CFB ≥ MID)

Note: CFB = change from baseline.

Differences between treatment groups in the EORTC QLQ-C30 subscales, the global health status/QOL score and EORTC QLQ-EN24 subscales will be evaluated using published minimally important difference (MID) as shown in Table 7.2. At each visit up to cycle 12 and by treatment, present the number and percentage of patients for each of the following categories for each subscale scores:

- Worsened: EORTC QLQ-C30 functional scores, global health status/QOL score, EORTC QLQ-EN24 score : change from baseline ≤ -MID, for symptom scores: change from baseline ≥ MID.
- Improved: EORTC QLQ-C30 functional scores, global health status/QOL score, EORTC QLQ-EN24 score: change from baseline ≥ MID, symptom scores: change from baseline ≤ -MID.
- Stable: change from baseline within MID.

In addition, at each visit and by treatment, the cumulative number and cumulative percentage whose change from baseline of the subscale scores reflects improvement will be summarized.

7.10.3 Time to Deterioration

Time to deterioration is defined as the time from the date of randomization to the date of first detection of deterioration for each EORTC QLQ-C30 subscales, the global health status/QOL score, and for each EORTC QLQ-EN24 score [date of first detection of deterioration – date of randomization + 1]. Deterioration is defined as a change from baseline ≥ MID for EORTC QLQ-C30 symptom scores and as a change from baseline ≤ -MID for EORTC QLQ-C30 function scores, global health status/QOL score and EORTC QLQ-EN24 score (see Table 7.2). Patients without deterioration will be censored at their last quality of life assessment. For patients with no post-baseline assessment, time to deterioration will be censored at Day 1.

The Kaplan-Meier method will be used to analyze the distribution of time to deterioration for each treatment arm. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs), hazard ratio estimated using Cox regression model with treatment arm and stratification factors as covariates along with associated 95% CI for comparison of paclitaxel to paclitaxel+MLN0128, paclitaxel to MLN0128 and paclitaxel to MLN0128+MLN1117, and Kaplan-Meier estimates at 6, 12, 18 and 24 months will be presented. A stratified log-rank test will be performed to compare the time to deterioration between treatment arms. The stratification factors are the histological subtype (endometrioid vs. non-endometrioid), the lines of prior chemotherapy (1 vs. 2) and prior taxane therapy (yes vs. no). The original IRT stratification factors will be used in models.

7.11 Safety Analysis

All safety analyses will be performed using the Safety population.

7.11.1 Adverse Events

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

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

Tabular summaries by MedDRA system organ class and preferred term will be provided for the following:

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

Patients reporting the same event more than once will have that event counted only once within each 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 inflammation	
	Mucosal membrane hyperplasia	
	Mucosal necrosis	
	Mucosal pain	
	Mucosal pigmentation	
	Mucosal roughness	
	Mucosal toxicity	
	Mucosal ulceration	
	Mucous membrane disorder	
	Oedema mucosal	
	Mucosal infection	

Adverse event of interest	MedDRA Preferred Term
	Mucosal excoriation Erythroplasia Burning sensation mucosal Paraesthesia mucosal Leukoplakia Drug eruption Fixed eruption Mucocutaneous haemorrhage
Rash	Mucocutaneous rash Nodular rash Rash Rash erythematous Rash generalised Rash macular Rash maculo-papular Rash maculovesicular Rash morbilliform Rash papular Rash rubelliform Rash scarlatiniform Rash vesicular

7.11.1.1 Deaths

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

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

7.11.1.2 Clinical Laboratory Evaluations

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE version 4.03. The number and proportion of patients with shifts in NCI CTCAE toxicity grades 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, 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 worse post baseline (2 hours only) will be summarized for MLN0128 QW and MLN0128 + MLN1117 arms.

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) up to 12 cycles. Figures of mean actual values over time will also be generated for these clinical laboratory parameters (in SI units).

7.11.2 Vital Signs

The actual values and change from baseline for vital sign parameters including temperature, heart rate, systolic and diastolic blood pressure, and weight, will be summarized over time for each treatment arm up to 6 cycles.

7.11.3 12-Lead ECGs

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

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

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

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

7.11.4 ECOG Performance Status

Shifts from baseline to the worst post-baseline ECOG score will be tabulated by treatment arm up to 6 cycles.

7.12 Interim Analysis

As specified in the protocol

There will be 2 interim analyses with early stopping rules for futility in both the single-agent MLN0128 and MLN0128 + MLN1117 arms using the Bayesian predictive probability design. The endpoint for the interim analysis will be based on the number of patients who achieve complete or partial response of any duration, or stable disease ≥ 16 weeks as assessed by the investigator (clinical benefit at 16 weeks). The decision rule for the interim analyses is derived based on the following assumptions:

- Ineffective CBR-16 rate (Ho): 30%.
- Effective CBR-16 rate (Ha): 50%.
- Alpha = 10%; power = 80%.
- Prior Beta Distribution Parameters: $\alpha_0 = 0.30$, $\beta_0 = 0.70$.
- The probability of early termination under the null hypothesis is 77%.

Each interim analysis will be based on patients who have had the opportunity to complete a minimum of 4 cycles or have discontinued study drug before the end of Cycle 4. The data cut-off is when the 20th patient achieves end of Cycle 4 in the treatment arms single-agent MLN0128 and MLN0128 + MLN1117. For all patients, use data up to Cycle 4 for interim analysis. Based on the first 20 patients in each arm, 1 or both arms may be dropped if at most 6 patients experience clinical benefit at 16 weeks in each arm. After the first 30 patients in each arm have been evaluated following 4 cycles of treatment, 1 or both arms may be dropped if at most 10 patients experience clinical benefit at 16 weeks in each arm.

For the interim analysis CBR at 16 weeks is defined as the number of patients who achieve CR or PR at the end of cycle 2 or end of cycle 4, or have SD at the end of Cycle 2 and at the end of Cycle 4 (based on unconfirmed response.).

Futility analysis

An additional futility analysis will be performed when 50% of PFS events have occurred for the paclitaxel and paclitaxel+MLN0128 treatment arms. The decision rule is based on a Bayesian framework: posterior probability (true HR > **0.78** | observed HR) is greater than 70%. The futility criteria will be met if the observed PFS HR for the comparison of paclitaxel vs paclitaxel+MLN0128 at the interim analysis for futility is greater than or equal to 0.898.

7.13 Changes in the Statistical Analysis Plan

1. QOL instruments, EORTC QLQ-C30 and EORTC QLQ EN24, will be analyzed over time and not restricted to just change from baseline to end of study visit as stated in the protocol.
2. The Per-protocol population was added to the analysis populations.
3. 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.
4. 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 paclitaxel to paclitaxel+MLN0128, paclitaxel to MLN0128 and paclitaxel to MLN0128+MLN1117. The protocol did not explicitly state the model for estimating the HRs.
5. The secondary endpoints e.g. ORR, CBR, CBR-16 and DOR will be based on both confirmed and unconfirmed best overall response.
6. Added details for the sensitivity analyses based on IRC review of scans. The IRC will only be performed for Arms A (paclitaxel) and B (paclitaxel + MLN0128).

8.0 REFERENCES

None

9.0 APPENDIX

Appendix A: By-Subject Listings:

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

- Disposition of subjects.
- Demographic and other baseline characteristics (including stratification factors).
- Important protocol deviations (including flag to indicate deviations that excluded patients from the per protocol population).
- Concomitant medications.
- Follow-up anti-cancer therapy.
- TEAEs resulting in discontinuation of study drug.
- SAEs.
- Deaths and cause of death.
- Sparse PK data.
- RECIST response assessment and best overall response based on investigator assessment and IRC assessment [Arms A (paclitaxel) and B (paclitaxel + MLN0128) only].

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	07-Sep-2018 20:06 UTC
	Clinical Science Approval	07-Sep-2018 20:08 UTC
	Biostatistics Approval	07-Sep-2018 21:23 UTC