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STATISTICAL ANALYSIS PLAN

RAMP: A Phase 1b, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral **R**ucaparib in Combination with Other **A**nticancer Agents in Patients with **M**etastatic Castration-Resistant **P**rostate Cancer

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ABBREVIATIONS AND SPECIALIST TERMS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
BRCA1/2	breast cancer gene 1 or 2
Clovis Oncology, Inc.	Clovis Oncology
C_{min}	minimum concentration
CR	complete response
CRM	cohort review meeting
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
GCSF	granulocyte colony-stimulating factor
HRR	homologous recombination repair
IV	intravenous
LD	longest diameter
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
PT	Preferred Term

RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SD	stable disease
SI	International System of Units
SOC	System Organ Class
StD	standard deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
v	version
vs	versus
WHO	World Health Organization

1 INTRODUCTION

This SAP describes the statistical analyses and data summaries to be performed to assess the safety, efficacy, and PK of rucaparib (CO-338) for Clovis Oncology sponsored clinical study CO-338-107, entitled "RAMP: A Phase 1b, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral **R**ucaparib in Combination with Other **A**nticancer Agents in Patients with **M**etastatic Castration-Resistant **P**rostate Cancer."

2 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

2.1 Study Design

The most recent version of the protocol (Amendment 1, dated 14 December 2020) indicates that this is a Phase 1b, open-label study with multiple treatment arms evaluating the PK, safety, tolerability, and preliminary efficacy of rucaparib in combination with androgen receptor (AR)-directed therapy (enzalutamide [Arm A] and abiraterone [Arm B]) in patients with mCRPC. Each arm consists of an initial PK, safety and tolerability assessment. Once completed, additional patients were to be evaluated to better characterize the PK, safety/tolerability and preliminary efficacy of the combination in an expansion phase.

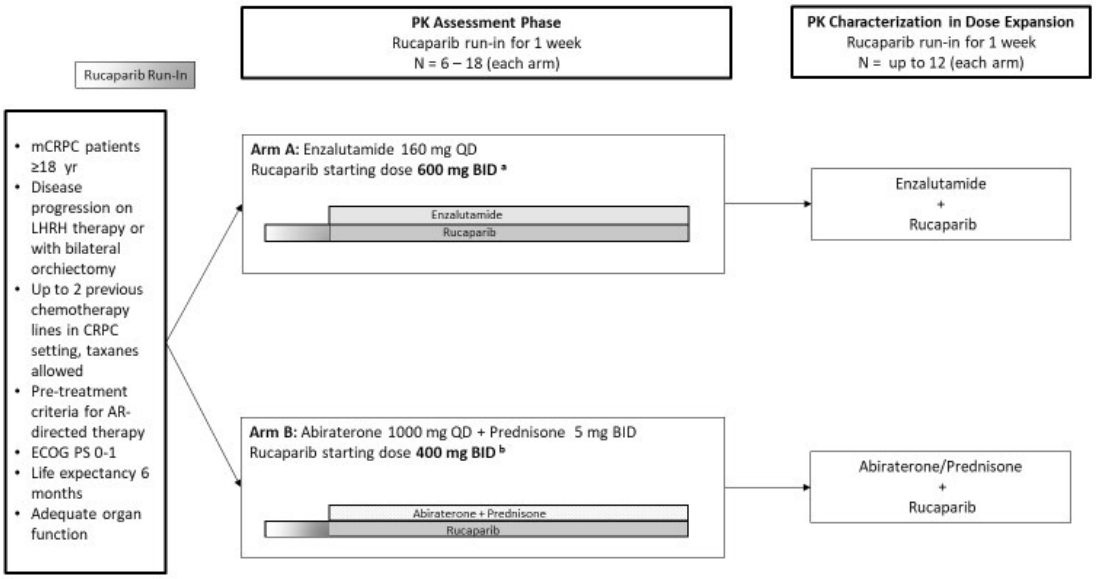
This study consists of a Screening Phase, a 1-week run-in period, a PK/DLT assessment phase, a Treatment Extension Phase (if applicable), and a Post-treatment Phase. Subjects start with a 1-week run-in period with rucaparib alone, followed by continuous 28-day treatment cycles of rucaparib and enzalutamide in combination. The PK/DLT assessment period in Arm A is across Cycles 1 and 2.

Prior to enrollment of patients, the decision was made to prioritize Arm A and not enroll into Arm B, so this SAP will only address Arm A. Furthermore, as this is an uncontrolled study not designed to establish efficacy, an abbreviated CSR will be provided to summarize results from Arm A.

2.2 Study Schema

The study schema in Figure 1 summarizes the treatment design of the study.

Figure 1 Study Schema



Abbreviations: AR = androgen receptor; BID = twice a day; CRPC = castration-resistant prostate cancer; DLT = dose-limiting toxicity; ECOG PS = Eastern Cooperative Oncology Group performance status; LHRH = luteinizing hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; PK = pharmacokinetic; QD = once a day.

[a] Rucaparib dose may be reduced to < 600 mg BID if more than one patient experiences a DLT. If rucaparib exposure is lower than expected with co-administration of enzalutamide, rucaparib dose may be increased proportional to the decrease in exposure, to a maximum of 1,000 mg BID.

[b] Rucaparib dose will be escalated from 400 mg BID to 600 mg BID, with a possible de-escalation to 500 mg BID. The dose of rucaparib may also be increased if there is unexpected lower exposure with coadministration of abiraterone, similar to the approach described for Arm A

2.3 Study Objectives and Endpoints

Table 1 Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
To evaluate the PK, safety and tolerability of rucaparib in combination with enzalutamide for mCRPC.	• Minimum concentration (C_{min}) of rucaparib and its metabolite M324. • Safe and tolerable dose of rucaparib in combination with enzalutamide for mCRPC
Secondary Objectives	**Secondary Endpoints**
To evaluate the preliminary efficacy of rucaparib with enzalutamide	• Best overall response as assessed by investigator summarized by ORR (as measured by mRECIST v1.1/ PCWG3 criteria; Appendix 1) at the optimal combination dose in each arm. • Change from baseline PSA levels
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the PK of enzalutamide in combination with rucaparib.	Cmin of enzalutamide (and metabolites N-desmethyl enzalutamide)
To assess the relationship between genomic alterations detected in tissue or blood with clinical outcomes to treatment	Association between genomic alterations and ORR and PSA responses
To assess the relationship between changes in circulating tumor DNA (ctDNA) profiles over time and clinical outcomes to treatment	Changes in genomic alterations as assessed by ctDNA over time

2.4 Sample Size Justification

The total enrollment planned for the PK/DLT portion of the study was between 6 and 18 patients for Arm A (rucaparib & enzalutamide combination) to allow evaluation of PK and safety parameters.

3 GENERAL ANALYSIS CONVENTIONS

Quantitative variables will typically be summarized using frequencies and percentages for appropriate categorizations and may also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following will be presented: N, mean, StD, median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages.

Baseline is defined as the last measurement on or prior to the first dose of rucaparib administration, unless otherwise specified.

PK analysis will be conducted using R (version 1.2.5033 or above). All other statistical analyses will be conducted with the SAS® System, Version 9.4 or higher.

3.1 Analysis Populations

The following analysis populations are defined for the study:

PK-evaluable Population: The PK Population will consist of all patients who received at least 1 dose of either rucaparib or enzalumatide and had at least 1 measurable concentration.

Safety Population – The Safety Population will include all patients who received at least 1 dose of rucaparib or 1 dose of enzalutamide.

DLT-evaluable Population: – The DLT-evaluable Population will consist of all patients who completed at least 70% of the scheduled doses of both rucaparib and enzalutamide and completed Cycles 1 and 2 of treatment, or who experienced a DLT in Cycles 1 or 2.

Efficacy Population: The Efficacy Population will consist of all patients evaluable for response by mRECIST/ PCWG3 criteria, or for PSA response, and could be subdivided into the RECIST-evaluable Efficacy Population and the PSA-evaluable Efficacy Population.

4 PATIENT DISPOSITION

Patient disposition will be summarized using frequency counts and the corresponding percentages. The number of patients in each analysis population, number of patients discontinued, and the primary reason for treatment discontinuation will be summarized.

5 PROTOCOL DEVIATIONS

The number of patients with major protocol deviations (eg, inclusion or exclusion criteria) will be determined prior to data base lock and will be summarized with frequencies and percentages or provided in a patient listing.

Protocol deviations will not be used to exclude any patients from the efficacy analyses.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographic and baseline characteristics will be summarized for the Safety Population.

6.1 Demographics

The demographic variables will be summarized with frequency tabulations and descriptive statistics. The demographic variables presented will include but not be limited to the following variables:

- Age (years): ≤ 50, 51-60, 61-70, 71-80, 81-90, > 90;
- Race: American Indian or Alaska Native, Asian, Black, Native Hawaiian or Pacific Islander, White, Other, Not Reported;
- Ethnicity: Hispanic, Not Hispanic;
- Height (cm): ≤ 75, > 75-100, > 100-125, > 125-150, > 150-175, > 175;
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150;
- BMI (kg/m^2);
- Baseline ECOG performance status score: 0, 1

6.2 Baseline Clinical Characteristics

The following variables will be summarized:

- Time since diagnosis of primary tumor (months): 0 to 12, 13 to 24, > 24;
- Number of prior lines of AR-directed therapy in a CRPC setting;
- Number of prior lines of chemotherapy in a mCRPC setting;
- Deleterious mutations in BRCA1/2 or other HRR genes;
- Status (germline or somatic) of mutation in BRCA1/2 or other HRR gene

Frequency tabulations and descriptive statistics will be presented as appropriate. Other baseline characteristic variables of interest may also be summarized if deemed appropriate.

6.3 Medical History

Medical history events will be classified using the MedDRA classification system version 20.1 or more recent. Medical history data will be listed.

7 DOSE-LIMITING TOXICITIES

A patient listing of all DLTs will be provided for the patients in the DLT-evaluable Population. A DLT is defined at any of the following events occurring in Cycle 1 or 2, according to CTCAE v5.0:

- Grade 3 or greater febrile neutropenia (ie, fever > 38.3°C with ANC < 1.0×10^9/L) of any duration or Grade 4 neutropenia lasting more than 7 days despite GCSF administration
- Grade 3 thrombocytopenia (platelets < 50×10^9/L) with significant bleeding or Grade 4 thrombocytopenia (platelets < 25×10^9/L) ≥ 5 days duration;
- Grade 4 anemia (ie, life-threatening consequences; urgent intervention indicated);
- Any nonhematological AE ≥ Grade 3, with the exception of:

- Nausea, vomiting, and diarrhea well controlled by systemic medication and with duration ≤ 72 hours;
- Fatigue;
- Grade 3 ALT or AST not accompanied by concomitant increase in total bilirubin above the ULN. Note: any Grade 4 ALT/AST is a DLT;
- Grade 3 arthralgia treated with non-steroidal anti-inflammatory drug(s) (or equivalent) that resolves to ≤ Grade 2 within 14 days
- Alopecia of any grade.

8 STUDY DRUG EXPOSURE AND COMPLIANCE

The following variables will be summarized:

- Duration of treatment (days, months)
- Number of dose reductions
- Number of treatment interruptions

Duration of treatment will be calculated as 1+ the number of days from study drug start date to date of study drug discontinuation. It will also be converted to months (#days/30.4375) and presented. Descriptive statistics and frequencies/percentages for appropriate categorizations will be used to summarize study drug exposure variables.

9 PRIOR AND CONCOMITANT MEDICATIONS

All concomitant treatments documented during the study period will be listed. Prior/concomitant medication coding will utilize WHO Drug version WHODrug Global B3 202003 or more recent.

A separate data listing of prior medications will be provided. Prior medications will be defined as those medications with both a start and a stop date that is before the day of the first dose of study drug administration. If either the start date and/or the stop date of the medication is missing so that it is unclear whether the medication was stopped prior to first dose of study drug administration, then the medication will be included in the concomitant medications listing.

10 EFFICACY ANALYSIS

Efficacy analyses will be performed using the Efficacy Population.

Response to treatment according to mRECIST/ PCWG3 and best overall response as assessed by the investigator will be listed.

PSA response will be listed and presented in a spider plot.

11 EXPLORATORY ANALYSIS

Exploratory analyses will not be included.

12 PHARMACOKINETIC ANALYSIS

The PK analysis will be performed on the PK-evaluable Population.

Rucaparib and M324 concentrations, as well as M324/rucaparib concentration ratio vs time profiles will be plotted for each patient. Effect of enzalutamide on rucaparib and/or M324 PK will be evaluated by comparing the trough PK data and the M324/rucaparib concentration ratio during the 7-day run-in period and the trough PK data in combination with enzalutamide. A drug-drug interaction (DDI) due to CYP3A4 induction by enzalutamide can be suggested if there is a decrease in rucaparib PK, and/or an increase in M324 PK or an increase in the M324/rucaparib concentration ratio. Mean PK plots may be provided if there are limited dose modifications.

Due to the limited data (ie, trough concentrations only, dose modifications), formal noncompartmental PK analysis is not planned.

13 SAFETY ANALYSIS

The safety analyses will be performed using the Safety Population. Tabulated AEs will at a minimum be presented as ‘Rucaparib Only’ (first 7 days on study) or ‘Rucaparib and Enzalutamide’.

13.1 Adverse Events

AEs will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI-CTCAE v5.0 or higher whenever possible. TEAEs are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days. AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

The number and percentage of patients who experienced TEAEs for each SOC and PT will be presented. Multiple instances of the TEAE in each SOC and multiple occurrences of the same PT are counted only once per patient. The number and percentage of patients with at least 1 TEAE will also be summarized.

The incidence of TEAEs will also be summarized by relationship to study drug according to the following categories: “treatment-related,” or “not treatment-related”. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once, as a relationship category of treatment-related.

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a

missing toxicity grade will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least 1 TEAE of the given grade will be summarized.

Separate tables including but not limited to the following, will be presented:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs will be included in the following 3 categories of relatedness: related to rucaparib, related to enzalutamide, and related to either study drug. Relatedness will be analyzed overall and by categories: CTCAE grade, Grade 3 or greater, resulting in dose reduction, resulting in treatment interruption, resulting in treatment discontinuation, outcome of death;
- Serious TEAEs, overall and by categories: age, sex, and treatment-relatedness (as defined above);
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication of either study drug;
- TEAEs resulting in interruption of study medication of either study drug; and
- TEAEs resulting in reduction, delay, or interruption of study medication of either study drug.

Non-TEAEs (pre-treatment and post-treatment) will be presented in the by-patient data listings for the safety population.

13.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will generally be presented in International System (SI) units. The on-treatment period will be defined as the time from first dose to 28 days after the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include shift tables based on CTCAE for shifts in grade from baseline to maximum, minimum, and last value during the on-treatment period. Additional listings will be presented as listing.

13.3 Vital Signs

Vital signs, including change from baseline calculations, will be listed.

14 STATISTICAL / ANALYTICAL ISSUES

14.1 Handling of Dropouts or Missing Data

All data will be used to their maximum possible extent, but without any imputations for missing data.

14.2 Pooling of Centers in Multi-Center Studies

All centers will be pooled for analysis.

14.3 Multiple Comparison / Multiplicity

No statistical comparisons will be performed.

14.4 Examination of Subgroups

Analyses of primary, secondary, and exploratory endpoints may be analyzed by baseline demographics and clinical characteristics listed in Section 6.1and Section 6.2 or for other subgroups of interest as appropriate.

14.5 Interim Analyses and Data Monitoring

No formal interim analysis occurred. Cohort Review Meetings (CRMs) were held throughout the study, and appropriate safety and PK analyses were provided prior to the meetings as applicable. Data were monitored and reviewed on an ongoing basis by the sponsor and investigators.

14.6 Analysis Included on ClinicalTrials.gov

Because enrollment was halted early with fewer than 20 subjects enrolled, only the primary endpoint will be included in ClinicalTrials.gov analyses.

15 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45(2):228-47.
2. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016.

16 APPENDICES

Appendix 1 Modified Response Evaluation Criteria In Solid Tumors v1.1 and Prostate Cancer Working Group 3 Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer et al. 2009[1] and at http://www.eortc.be/Recist/Default.htm. and PCWG3 criteria as described by Scher, et al. 2016[2]

A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- A minimum size of 20 mm by chest X-ray

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

For the purposes of this study, bone metastatic lesions should be recorded at baseline and followed during treatment using PCWG3 criteria. Bone lesions should not be recorded as target or nontarget lesions according to mRECIST criteria.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ (per PCWG3), representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Nontarget Lesions

RECIST Version 1.1 criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a $\leq$ 5 mm contiguous reconstruction algorithm. If a site can document that the CT performed as part of a positron emission tomography (PET)/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Ultrasound, endoscopy and laparoscopy should not be used to measure tumor lesions.

Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new extra-skeletal lesions is also considered progression. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of 1 or more new extra-skeletal lesions and/or unequivocal progression of existing nontarget lesions. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Evaluation of Best Overall Response: Patients with Target (± Non-Target) Disease			
Target Lesions	**Nontarget Lesions**	**New Lesions[a]**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] New bone metastatic lesions should not be considered as a 'Yes' response; only new extra-skeletal lesions.

Evaluation of Best Overall Response: Patients with Non-Target Disease Only		
Nontarget Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual

lesion be investigated (fine-needle aspiration/biopsy) prior to confirming the complete response status.

Confirmation

If an initial CR or PR is noted, confirmatory scans must be performed at least 4 weeks later**.**

Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started), including progression in bone per PCWG3 criteria.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

PCWG3 Criteria for Assessment of Bone Disease

PCWG3 criteria will be used to document evidence of disease progression in bone lesions as described by Scher, et al. 2016[2]

Imaging of Baseline Bone Disease

The use of bone scan as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a study.

Different modalities for imaging bone metastases can provide different information for the same patient. However, because of the lack of standards for reporting disease presence or changes after treatment, PET imaging with sodium fluoride, fluorodeoxyglucose, choline, or prostate-specific membrane antigen, bone marrow MRI (body MRI), and other modalities that are in use to image bone, should be approached as new biomarkers subject to independent validation.

Criteria for progression in bone at study entry

- Two new lesions observed on 99mTc-methylene diphosphonate radionuclide bone scintigraphy
- Confirm ambiguous results by other imaging modalities (eg, CT or MRI) however only positivity on the bone scan defines metastatic disease to bone

Documentation of baseline bone disease

- Presence or absence of metastasis recorded first
- A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area, is required
- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial

Following for bone progression during the study

- Exclude pseudoprogression in the absence of symptoms or other signs of progression
- At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2 + 2 rule)
- If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented
- For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
- Date of progression is the date of the scan that first documents the second lesion
- Changes in intensity of uptake alone do not constitute either progression or regression