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**Statistical Analysis Plan**

Study code PrE0102

Version FINAL

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**Randomized, Double-Blind, Placebo-Controlled Phase II Trial of Fulvestrant (Faslodex) plus Everolimus in Post-Menopausal Patients with Hormone-Receptor Positive Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy**

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Title:	Randomized, Double-Blind, Placebo-Controlled Phase II Trial of Fulvestrant (Faslodex) plus Everolimus in Post- Menopausal Patients with Hormone-Receptor Positive Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy
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## 1. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE(s)	Adverse Events(s)
SAP	Statistical Analysis Plan
CSR	Clinical Study Report
AI	Aromatase Inhibitor
ITT	Intention-to-Treat
QDS	Quality Data Services
QD	Once Daily
CTCAE	The CTEP Common Terminology Criteria for Adverse Events (CTCAE)
PFS	progression-free survival
RECIST	Response Evaluation Criteria in Solid Tumors
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CR	Complete Response
SD	Stable Disease
PR	Partial Response
PD	Progressive Disease
CSR	clinical study report
WHO- DD	World Health Organization Drug Dictionary
TEAEs	Treatment-emergent AEs
MedDRA	Medical Dictionary for Regulatory Activities
ICH	International Conference on Harmonization
US	United States

## **2. INTRODUCTION**

### **2.1. Objective of the Abbreviated Statistical Analysis Plan**

This abbreviated statistical analysis plan (SAP) describes the planned analysis of the safety and efficacy data from the study to be prepared for a publication based on an outline provided by sponsor (Appendix 1). A detailed description of the planned tables, figures and listings (TFLs) to be prepared for the publication is provided in the accompanying TFL template document.

The intent of this document is to provide guidance for the analysis of data related to safety and efficacy to describe any applicable statistical procedures. In general, the analyses come directly from the protocol, unless they have been modified by agreement between the Sponsor and Quality Data Services, Inc. (QDS). A limited amount of information concerning this study (e.g., objectives, study design, treatment schedule, variables and endpoints) is summarized to help the reader interpret the accompanying TFL templates. This abbreviated SAP includes details about the variables and endpoints considered for the publication. The SAP also includes clarifications for analysis population (changes from protocol specified definitions), additional endpoints and sensitivity analyses not specified in the protocol but required for the publication. Attached signatures indicate approval of the statistical analysis sections of the SAP, as well as accompanying TFL templates. These sections must be agreed upon prior to database lock. Any revisions to statistical analyses required for the publication will be document in SAP Amendment (s). Any revisions to planned TFLs which do not require revisions to SAP will be documented in a Note to SAP.

## **3. STUDY OBJECTIVES**

### **3.1. Primary Objective**

To assess progression-free survival in post-menopausal patients with hormone-receptor positive metastatic breast cancer that is resistant to aromatase inhibitor (AI) therapy treated with fulvestrant and everolimus compared to fulvestrant alone.

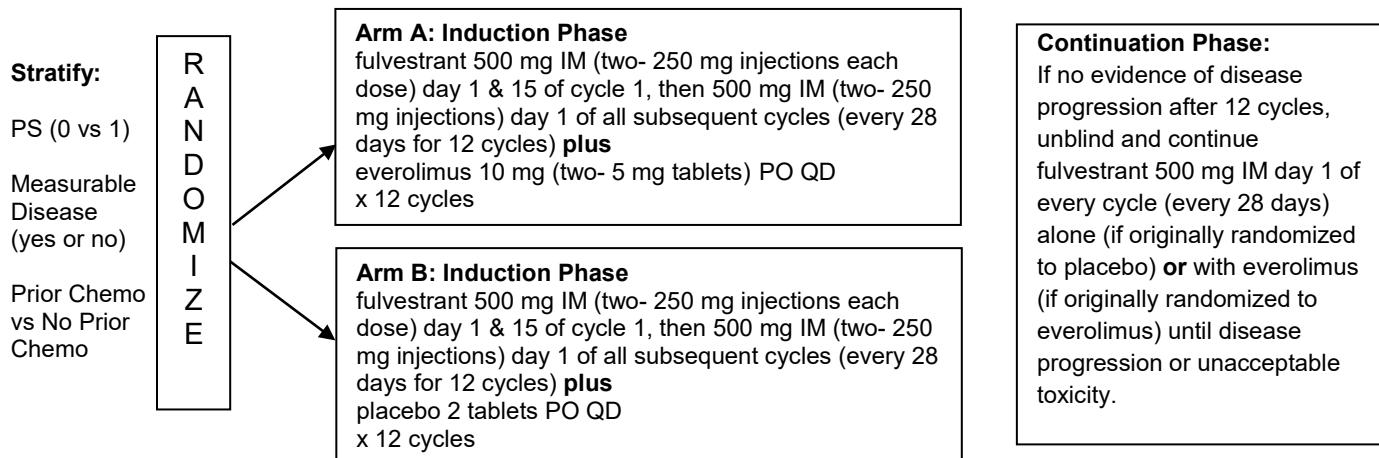
### **3.2. Secondary Objectives**

To describe the safety profile, objective response rate, time to progression and overall survival in post-menopausal patients with hormone-receptor positive metastatic breast cancer that is resistant to aromatase inhibitor (AI) therapy treated with fulvestrant and everolimus compared to fulvestrant alone

## 4. STUDY DESIGN

### 4.1. General Study Design and Plan

This is a randomized, double-blind, placebo controlled Phase II study. Approximately 130 subjects will be enrolled at 25 centers within the US. Subjects will be randomized (1:1) to receive everolimus or placebo after consideration of stratification factors of performance status (0 vs.1), measurable disease (with or without non-measurable) vs. non-measurable disease, and prior chemotherapy for metastatic disease vs. no prior chemotherapy. The treatment plan is defined below.



Note: 1 cycle = 28 days

### 4.2. Study Population

Subjects enrolled in the study must be postmenopausal and have stage IV disease or inoperable locally advanced disease. They must have ER and/or PR-positive disease as determined by their local pathology or reference laboratory by ASCO-CAP criteria. Tumors must be HER-2/neu negative or equivocal by standard ICH/FISH or ICH/CISH methodologies by ASCO-CAP criteria. Subjects must be Aromatase Inhibitor resistant, defined as:

- relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or,
- progressive disease while receiving an aromatase inhibitor for metastatic disease

### 4.3. Treatment Administration and Duration of Therapy

Subjects must not start protocol treatment prior to randomization. Treatment is to begin within 7 working days of randomization, and includes two phases: induction phase and continuation phase.

During the Induction Phase, subjects will receive:

- fulvestrant 500 mg IM (two-250 mg injections per dose) on day 1 & 15 of Cycle 1, then 500 mg IM (two-250 mg injections) on day 1 of all subsequent cycles (every 28 days) plus everolimus 10 mg (two- 5 mg tablets) PO daily, OR
- fulvestrant 500 mg IM (two-250 mg injections per dose) on day 1 & 15 of Cycle 1, then 500 mg IM (two-250 mg injections) on day 1 of all subsequent cycles (every 28 days) plus placebo two tablets PO daily

(as randomized).

Subjects will be treated for a maximum of 12 cycles with fulvestrant plus everolimus/placebo during the Induction Phase. Induction treatment continues until there is evidence of progressive disease or unacceptable toxicity for a maximum of 12 cycles (as defined in Protocol Section 5.6). Subjects with no evidence of progressive disease who remain on study **after completing** 12 cycles of the Induction Phase are unblinded and proceed to the Continuation Phase. Subjects in the Continuation Phase will continue to receive fulvestrant alone (if originally randomized to placebo) **or** in combination with everolimus (if originally randomized to everolimus) until disease progression or unacceptable toxicity. Subjects in both the Induction and Continuation Phases will have tumor measurements performed every 12 weeks (+/- 1 week).

Protocol therapy will be discontinued for progressive disease at any time. Subjects are free to halt therapy at their request. Treatment may be discontinued if intercurrent co-morbidities occur, which, in the opinion of the treating physician, would preclude safe administration of study drugs.

Subjects who discontinue everolimus/placebo because of suspected everolimus-associated toxicity should continue treatment with fulvestrant alone until disease progression. In unusual circumstances where fulvestrant must be discontinued prior to disease progression due to intolerable fulvestrant-associated toxicity, the medical monitor should be contacted. All subjects who have discontinued protocol therapy will be followed for survival and for progression, even if protocol therapy was discontinued because of toxicity or for other reasons. All surviving subjects who have discontinued induction protocol therapy (fulvestrant and everolimus/placebo) for any reason will be followed for 30 days for study drug related (fulvestrant and/or everolimus/placebo) toxicities to  $\leq$  grade 1 (or if  $>$ grade 1, event must be permanent and stable).

#### **4.4. Dose Modifications and Toxicity Management**

Dose modifications for all drugs will be made using the general guidelines included in Protocol Section 5 (Tables 5-0, 5-1 and 5-2) and summarized below:

- All dose reductions are permanent. Fulvestrant will not be dose reduced.
- Regardless of the reason for holding any study drug treatment, the maximum allowable length of treatment interruption is  $\leq$  3 weeks. If the delivery of any study drug due to toxicity is delayed for more than 3 weeks, that drug should be permanently discontinued.
- No more than 2 dose reductions for everolimus/placebo will be allowed. Further need for dose reduction will result in discontinuation of that drug.
- If dose is delayed due to toxicity, labs/toxicity should be reevaluated at least weekly until recovery to treatment levels, or as indicated in the dose modification tables.
- Subjects who discontinue everolimus/placebo because of suspected everolimus-associated toxicity should continue treatment with fulvestrant alone until disease progression.
- In unusual circumstances where fulvestrant must be discontinued prior to disease progression due to intolerable fulvestrant-associated toxicity, the Medical Monitor should be contacted.

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Toxicity management is defined in Section 5 of the protocol.

#### **4.5. Withdrawal of Subjects from Study**

Subjects are to be discontinued from study therapy and be withdrawn from the study for the following reasons:

- Withdrawal of the subject's consent (subject's decision to withdraw for any reason)
- Termination of the study by PrECOG
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Inability to comply with protocol
- Discretion of the investigator
- Disease progression (subject will be followed for survival)

#### **4.6. Study Schedule of Assessments**

Study schedule of assessments is included in Appendix 2.

## 5. MEASUREMENT OF EFFECT

### 5.1. Evaluation of disease

For the purposes of this study, subjects should be re-evaluated for response every 12 weeks, +/- 1 week. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before randomization.

Response and progression are to be evaluated using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1). For measurable disease, changes in the sums of the longest diameters (unidimensional measurement) of the tumor lesions and the shortest diameters in the case of malignant lymph nodes are used in the RECIST criteria. For subjects without measurable disease, disappearance of disease, unequivocal progression, or the absence of either will be used to assess response. Further details and methods of evaluation of disease are included in Protocol Sections 6.1.2-6.1.3 and in SAP Appendix 3.

### 5.2. Response Criteria

Details about Response Criteria for target, non-target and new lesions are included in Protocol Sections 6.1.4.1, 6.4.1.2, 6.4.1.3, and in SAP Appendix 4.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Since response is not the primary endpoint, no confirmation of response is required in this study. See Protocol Section 6.1.4.4 and SAP Appendix 5.

### 5.3. Efficacy Measurements Definitions

Efficacy measurements include progression-free survival (PFS), overall survival, and time to progression, objective response rate, clinical benefit rate (CBR), duration of overall response (CR), duration of overall CR, and duration of stable response.

Progression-free survival (PFS) is defined as the duration of time from time of randomization to time of progression or death, whichever occurs first. A subject who has neither progressed nor died will be censored on the date of last tumor assessment.

Overall Survival (OS) is defined as the time from randomization until death or censored at the date of last follow-up.

Time-to-progression (TTP) is defined as the time from randomization until progression of the disease. Patients without progression will be censored at the date of last tumor assessment.

Objective response rate is defined as the proportion of subjects with best overall response of CR (complete response) or PR (partial response).

Clinical benefit rate (CBR): is defined as the proportion of subjects with best overall response of CR (complete response) or PR (partial response) or with stable disease (SD) for at least 24 weeks.

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 progressive disease is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

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

Duration of stable disease: Stable disease 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, including the baseline measurements.

## 6. SAFETY MEASUREMENTS

Safety is to be evaluated by

- Adverse events
- Clinical laboratory tests,
- Physical examination findings,
- Vital signs measurements,

The following sections include details and definitions for the safety measurements to be summarized per list of TLFs included in Appendix 1.

### 6.1. Adverse Events

Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed).

Treatment-emergent AEs: any adverse event starting on or after the first treatment dose.

AE Severity:

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be utilized for AE reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

All appropriate treatment areas should have access to a copy of the CTEP CTCAE Version 4.0 (see Protocol Appendix E)

AE Attribution (Relationship)

The following categories and definitions of causal relationship or attribution to study drug should be used to assess Adverse Events:

- Definite: There is a reasonable causal relationship between the study drug and the event. The event responds to withdrawal of study drug (dechallenge) and recurs with rechallenge, if clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the event. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is a reasonable causal relationship between the study drug and the event. Dechallenge information is lacking or unclear.
- Unlikely: There is doubtful causal relationship between the study drug and the event.
- Unrelated: There is clearly not a causal relationship between the study drug and the event or there is a causal relationship between another drug, concurrent disease, or circumstances and the event.

Categories 'Definite', 'probable' and 'possible' are considered study drug related. Categories 'not likely' and 'not related' are considered not study drug-related.

The development of a new cancer is to be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the subject into the clinical study.

A **serious AE** is any untoward medical occurrence occurring after informed consent is granted or that at any dose:

- results in death,

- is life-threatening (defined as an event in which the study subjects was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

#### Second Primary Cancers:

New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the subject into the clinical study.

All cases of new primary cancers that occur during or after the start of protocol treatment are to be reported to PrECOG within 30 days of diagnosis, regardless of relationship to protocol treatment. Secondary primary malignancies should also be reported as a SAE.

#### **6.2. Concomitant Medications**

Bone modifying medications taken during the study are to be recorded on eCRF .

## 7. GENERAL STATISTICAL CONSIDERATIONS

Statistical analysis and programming of tables and listings will be conducted by QDS, using SAS® Release 9.2 (SAS Institute Inc., Cary, North Carolina, USA). After the TFLs are approved as final, SAS programs used to perform statistical analyses and generate analysis datasets and TFLs will be archived in 2 formats (ASCII, and .PDF); the analysis SAS Datasets will be archived in XPT format created using SAS PROC XPORT.

The analyses described in this section are applicable for the planned TLFs listed in Appendix 1.

### 7.1. Methodology

Continuous data will be summarized with the following descriptive statistics: number of observations, mean, (n) standard deviation (StdDev), median, minimum (min), and maximum (max). Categorical data will be summarized with frequencies and percentages.

Listings will be presented by subject and all data will be presented. Tables will be presented by treatment arms and only data pertaining to the specific population being analyzed will be used.

### 7.2. Analysis Populations

The protocol defines the following analyses populations:

Evaluable for toxicity: All treated subjects (defined as subjects who receive at least one dose of fulvestrant or everolimus/placebo) are evaluable for toxicity from the time of their first treatment with fulvestrant and everolimus/placebo. All subjects are to be followed for 30 days for toxicity after the last dose of study therapy (fulvestrant and/or everolimus/placebo) or until recovery from all toxicity (to ≤ grade 1) attributed to study therapy, whichever is longer (or if >grade 1, event must be permanent and stable).

Evaluable for objective response: Subjects will be classified into two groups according to their measurable disease stratification level at randomization. Subjects with measurable disease (with or without bone only metastases) will have their responses classified according to the definitions stated in Protocol Section 6.1.2 and SAP Appendices 3 through 5. Subjects in this stratum who are unevaluable for objective response will be included in the denominator when calculating the response rate.

Evaluable for non-target disease response: Subjects who are stratified into the bone metastases only cohort at randomization will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions. Subjects who are free of new lesions and free of unequivocal progression will be considered to have clinical benefit.

Evaluable for efficacy: The primary efficacy analysis will be done including eligible, treated subjects.

Intent-to-treat (ITT) analysis population includes all subjects as randomized. Sensitivity analyses of efficacy will be done among all subjects as randomized (ITT population).

The next sections will indicate the required analysis population for the planned analyses. This is also documented in each TLF template.

### **7.3. Subject Disposition**

The following summary tables will be prepared to describe subjects' disposition and case status for all enrolled subjects:

#### **7.3.1. Accrual by Institution**

Number and percentage of subjects enrolled and ineligible will be summarized by study site overall. Number of randomized subjects, withdrawn before treatment, eligible and treated will be summarized by site and by randomized treatment arm. Percentages for ineligible will be based on all enrolled. Percentages for randomized subjects are based on all enrolled. Percentages for withdrawn before treatment, eligible and treated will be based on the number randomized within each treatment arm.

#### **7.3.2. Case Status**

Number and percentage of subjects enrolled and ineligible will be summarized overall. Number of randomized subjects, withdrawn before treatment, eligible and treated will be summarized by randomized treatment arm. Percentages for ineligible will be based on all enrolled. Percentages for randomized subjects are based on all enrolled. Percentages for withdrawn before treatment, eligible and treated will be based on the number randomized within each treatment arm.

Number and percentage of subjects who completed Induction phase, discontinued during induction phase, were unblinded during induction phase, continued in Continuation phase, completed study, and discontinued the study will be summarized by treatment arm and overall. Percentages are based on number of eligible and treated subjects.

Subject's reasons for discontinuation at the end of treatment will be summarized by the following categories: adverse events, death, progressive disease, symptomatic progression, physician decision, protocol non-compliance, withdrawal by subjects, study terminated by sponsor, or unknown. If there are still subjects on treatment at the time the clinical study report is prepared, an additional category "Remain on treatment" will be included. Percentages will be calculated based on number of eligible and treated subjects.

### **7.3.3. Reasons Subjects were Ineligible**

These will be summarized in a by subjects data listing including inclusion / exclusion criteria not met by subjects considered ineligible for the study

### **7.3.4. Reasons Subjects did not Start Treatment**

Per protocol, subjects are to start treatment within 7 days post randomization. Subjects who were randomized and discontinued study prior to starting treatment will be listed. This listing will include randomized subjects who discontinued prior to induction phase and do not have a corresponding record in EX domain or have only one record in EX domain indicating Fulvestrant or Everolimus/Placebo not administered. Reason for discontinuation will be based on End of Treatment CRF (DS domain).

### **7.3.5. Stratification Factors**

A summary of responses for the 3 stratification factors considered for randomization will be prepared by treatment arm and overall. The 3 factors are: performance status (1 or 0), measurable disease (yes or no), and prior chemotherapy (yes or no). This information will be based on IWR.

Since performance status is assessed again on Day 1 of Cycle 1, a cross-tabulation between performance status as reported and recorded in IWR and performance status as recorded on Day 1 Cycle 1 will be prepared (overall and by treatment group).

For both tables, percentages will be based on number of randomized subjects.

## **7.4. Subject Characteristics**

Demographic and baseline characteristics will be summarized overall and by treatment arm for randomized subjects. The following variables will be summarized:

- Age (years) as continuous variable
- Sex (female, male)
- Race categories
- Ethnicity categories
- Time since diagnosis (months) as continuous variable
- Number and percentage of subjects who developed locally recurrent disease
- Number and percentage of subjects who developed metastatic disease
- Time since recurrence / progression (months) as continuous variable

- Sites of recurrence of metastasis
- ER status
- PR status
- HER2 Neu and HER2Neu FISH results
- Prior anti-cancer therapies (Number of regimens)
- Prior bone-modifying medications (Number of regimens)

Time since diagnosis = (date of informed consent – date of diagnosis + 1)/30.4375.

Time since recurrence / progression = (date of informed consent – date of recurrence / progression + 1)/30.4375

Partial dates for date of diagnosis or for date of recurrence / progression will be imputed as follows:

- if the day is missing, it will be imputed it to be 15th of the month; for example, if date is recorded as JUL-1990, the imputed the date will be 15-JUL-1990;
- if the day and the month are missing, it will be imputed to 30-JUN; for example, if only 1976 is recorded, the imputed date will be 30-JUN-1976.

Percentages will be based on number randomized. Results will be summarized for all randomized subjects and for the Evaluable for Efficacy population (including eligible and treated subjects).

## 7.5. Dosing and Number of Cycles in the Study

The number of cycles of treatment received will be summarized by reason off treatment for all subjects evaluable for toxicity by treatment arm. The following rule will be applied: subjects who start treatment but discontinue during Cycle 1 will be reported for “reason off treatment” in Cycle 1; subjects who discontinue during Cycle 5 (for example) will be counted as “Completed Treatment” for cycles 1, 2 , 3, and 4 and under reason off treatment for Cycle 5.

Dose during Induction and during Continuation phase will be summarized as a continuous variable. Dose during a phase is computed as the average dose across all days when medication was taken (dosing interval). Dosing interval is the interval between the date of the first dose in the phase till the last dose date recorded in the diary. If during the dosing interval, dose modification indicates missed or dose withdrawn, the respective days are be counted with 0 mg.

## 7.6. Concomitant Medications

A by-subject data listing of bone modifying medications will be prepared for all treated subjects.

## 7.7. Efficacy Analysis

### 7.7.1. Response Analysis

Best overall response at the end of treatment will be summarized by treatment arm for all eligible, treated subjects. The summary table will include counts and percentages for each response category (CR, PR, SD, PD, unevaluable).

Objective response rate (defined as CR or PR among subjects with measurable disease) and clinical benefit rate (defined as CR, PR or SD for at least 24 weeks for subjects with measurable disease and as freedom from new lesions or unequivocal progression for at least 24 weeks among subjects with bone metastases only) will be estimated (n, %) for all eligible, treated subjects by treatment arm and disease stratum. The 90% exact binomial confidence interval for each of the three rates:

- Objective Response – Subjects with Measurable Disease
- Clinical Benefit – Subjects with Measurable Disease
- Clinical Benefit – Subjects with Bone Metastases Only

will also be included in the summary table. In the unlikely event that complete responses are observed among patients with bone metastases only, these will be described.

A by-subject data listing will be prepared to indicate the reason subjects were not evaluable for response. Include in this list subjects with:

- No re-evaluation of disease with Reason Unevaluable = No Re-evaluation of Disease. If subject discontinued study early, include reason for early termination in “Specify” column. If assessments were noted as “Not Done” at the time points/ visits prior to discontinuation, list visits when ‘not done’ and reason not done (one entry per time point).
- Re-evaluation of disease not done within required time frame
- Incomplete evaluation of disease (e.g., missing some target lesions that were evaluated at baseline).

### **7.7.2. Progression-Free Survival (PFS), Time-to-Disease Progression (TTP), and Overall Survival (OS)**

Median time and 90% confidence interval for PFS, TTP, and OS will be summarized for all eligible, treated subjects by treatment arm using Kaplan-Meier estimates. If medians have not been reached, 2-year PFS, TTP and OS should be reported instead, with 90% confidence intervals, calculated using time-to-event methods.

PFS = time from randomization to documented disease progression or death.

TTP = time from randomization until progression of disease

OS = time from randomization until death.

Subjects who are lost to follow-up are censored at the time of last tumor assessment for TTP and PFS and at the time of the last known contact for OS. All other subjects are censored at the time of analysis.

In addition to the summary table, PFS and OS will be displayed by treatment arm using Kaplan-Meier survival curves.

As a sensitivity analysis, all of the above analyses described in Section 7.6.2 will be repeated for the as-randomized population (intent-to-treat analysis).

## **7.8. Safety Analysis**

### **7.8.1. Adverse Events**

Adverse events (AEs) will be graded using CTC Version 4, coded using MedDRA dictionary version 16.0, and flagged as treatment emergent if start date of the adverse event is on or after Cycle 1 Day 1 dosing. For adverse events with partial start date (i.e., with only month and year are recorded), the following imputation rule will be applied: 15<sup>th</sup> of the month or first dose date, whichever comes later.

All AEs and treatment-related AEs will be summarized for all treated subjects by toxicity grade and by treatment arm.

AEs with relationship reported as 'Definite', 'probable' and 'possible' are considered study drug related. AEs with relationship reported 'not likely' and 'not related' are considered not study drug-related. AEs with missing relationship will be considered study drug related.

The following by subject data listings will be prepared: subjects with serious adverse events, subjects with Grade 5 adverse events, and subjects with second primary cancer.

## **8. REPORTING CONVENTIONS**

The mean and median will be displayed to one decimal place greater than the original value and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using SAS® Release 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

The following standards will be used in the data presentation:

- Tables should be in landscape format. Output should adhere to US / International Conference on Harmonization (ICH) margins and should not require changes for European page size. A blank row will separate the header from the content of the table listing. For tables that have “n (%)", the placement should be centered below “N=xx" in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.
- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If "%" is part of the column heading, do not repeat the "%" sign in the body of the table. Unless specified otherwise, "%" should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, leave the corresponding percentage blank.
- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number.
- All data listings will be sorted by Subject Number and time point (if applicable).
- The date format for all dates is DDMMYY YYYY.

A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

## **9. REFERENCES**

References are provided in the protocol.

## **10. TABLES, FIGURES, AND LISTINGS**

See separate template document.

## 11. APPENDIX 1: LIST OF TABLES, LISTINGS AND FIGURES REQUESTED FOR PUBLICATION

*The following list of required TLFs was provided by PrECOG on 24 May 2013.*

PrE0102 Tables, Listings, Figures  
5/24/13

Table (1): Accrual by Institution

Table (2): Case Status (by arm and total):

Number Enrolled  
Number Ineligible  
Number Withdrawn before Treatment  
Eligible and Treated

Listing (1): Reasons ineligible

Listing (2): Reasons for not starting treatment

Table (3) of Stratification Factors (by arm and total)

Cross-tab (4) of Stratification Factors and Corresponding data from CRF (by arm and total)

Table (5): Subject Characteristics at Study Entry (by arm and total)

Table (6): Number Cycles of Treatment Received by Reason off Treatment (by arm)

Table (7): Dosing: Median and range dose during induction and continuation (by arm and agent)

Toxicity Tables (include all subjects receiving at least 1 dose of study drug/placebo. Count each subject once at the highest grade):

(8) All events, grade 1 to 5, regardless of attribution, by arm and grade

Count

Percent

(9) Treatment-related events, grade 1 to 5, by arm and grade

Count

Percent

Above 2 tables should use CTCAE terminology if possible

(10, 11) Same 2 tables, by System Organ Class rather than individual event

Listing (3) of Serious Adverse Events

Listing (4) of Subjects with Grade 5 Adverse Events

Table (12) of Best Overall Response, by response category and treatment arm, including unevaluable subjects as non-responders

Table (13): Objective Response rate and 90% exact binomial confidence interval, by arm, and Clinical Benefit Rate (CR+PR+SD) with 90% exact binomial confidence interval, by arm and both overall

List (5) of Subjects Unevaluable for Response, with arm and reason

Listing (6) of Second Primary Cancers

Table (14) showing PFS, TTP and OS: Median and 90% CI, or 2-year rates with 90% CI

Listing (7) of Bone Modifying Medications

Figure 1 – PFS by treatment arm

Figure 2 – OS by treatment arm

An additional listing for Bone Modifying Medication was requested via email on 11Jun2013.

For completeness, an additional table summarizing adverse events was included in TLF templates.

## 12. APPENDIX 2: SCHEDULED ASSESSMENTS

Procedure	Induction Phase (fulvestrant + everolimus or placebo for a maximum of 12 cycles)					End of Induction Phase <OR> End of Treatment Section 5.6 <sup>a</sup>	Continuation Phase <sup>e</sup> (until progression or unacceptable toxicity)	Follow-Up Off Therapy (every 3 months for total of 3 yrs from date of randomization)
	Pre-Study	Cycle 1 Day 1 <sup>*</sup>	Cycle 1 Day 15	Day 1 Each Subsequent Cycle <sup>*</sup>	Every 12 weeks			
Eligibility Assessment	X <sup>a</sup>							
Informed Consent	X <sup>a</sup>							
Medical History & Assessment of Baseline Signs and Symptoms	X <sup>a</sup>							
Physical Exam	X <sup>a</sup>	X <sup>b</sup>	X	X <sup>c</sup>		X		
Concomitant Meds (see Appendix C)	X <sup>a</sup>	X <sup>b</sup>	X	X <sup>c</sup>		X		
Vital Signs (Blood Pressure, Heart Rate, Temperature) and Weight	X <sup>a</sup> (includes Ht)	X <sup>b</sup>	X	X <sup>c</sup>		X		
ECOG Performance Status	X <sup>a</sup>	X <sup>b</sup>	X	X <sup>c</sup>		X		
Adverse Events Assessments		X <sup>b</sup>	X	X <sup>c</sup>		X <sup>h</sup>	X <sup>h</sup>	X <sup>h,m</sup>
Imaging Scans	X <sup>a,g</sup>				X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>g,k,m</sup>
PT with INR	X <sup>a</sup>							
Urinalysis	X <sup>a</sup>							
CBC with differentials, Platelets	X <sup>a</sup>	X <sup>b</sup>	X <sup>d</sup>	X <sup>c,d</sup>		X <sup>d</sup>	X <sup>i</sup>	
Serum Creatinine, Electrolytes (K, Na, Cl, CO <sub>2</sub> ), Ca, BUN, Bicarbonate, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium, Uric Acid.	X <sup>a</sup>	X <sup>b</sup>	X	X <sup>c</sup>		X	X <sup>i</sup>	
Fasting Glucose	X <sup>a</sup>	X <sup>b</sup>		X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>i</sup>	
Fasting serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL)	X <sup>a</sup>	X <sup>b</sup>		X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>i</sup>	

Procedure	Induction Phase (fulvestrant + everolimus or placebo for a maximum of 12 cycles)					End of Induction Phase <OR> End of Treatment Section 5.6 <sup>a</sup>	Continuation Phase <sup>b</sup> (until progression or unacceptable toxicity)	Follow-Up Off Therapy (every 3 months for total of 3 yrs from date of randomization)
	Pre-Study	Cycle 1 Day 1*	Cycle 1 Day 15	Day 1 Each Subsequent Cycle*	Every 12 weeks			
HBV- DNA, HbsAg, HBs Ab, HBc Ab, HCV- RNA-PCR	X <sup>a,f</sup>							
HBV DNA, HCV RNA-PCR		X <sup>f</sup>		X <sup>f</sup>			X <sup>i</sup>	
Study Drug Compliance (Pill Diary)			X	X		X	X <sup>j</sup>	
PFTs with DLCO as medically indicated <sup>l</sup>								

**a:** ≤ 4 weeks of randomization; if assessments required ≤ 7 days of Cycle 1 Day 1 (C1D1), they do not need to be repeated (includes labs).

**b:** ≤ 7 days prior to the start of C1D1.

**c:** ≤ 72 hour window allowed prior to D1 of each subsequent cycle after the first cycle for scheduled therapy/tests/visits. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

**d:** In the event of grade 3 or 4 hematologic toxicity, CBC with differential and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery.

**e:** ≤ 72 hrs prior to Cycle 2 Day 1 then approximately every 12 weeks during treatment (and more frequently as clinically indicated), and at end of treatment.

**f:** All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection. It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral (e.g., Lamivudine) for 1-2 weeks prior to receiving study drug (see Table 5-3). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of everolimus. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR. Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA ≤ 7 days prior to the start of C1D1 and ≤ 72 hrs prior to D1 of each subsequent cycle to monitor for reactivation. See Table 5-4 for reactivation instructions. Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on ≤ 7 days prior to the start of C1D1 and ≤ 72 hrs prior to D1 of each subsequent cycle to monitor for flare. Everolimus must be discontinued if HCV flare is confirmed according to the guidance in Table 5-5.

**g:** Tumor measurements may be made using physical examination, CT Scans or MRI. Tumor assessments will be performed every 12 weeks, +/- week (every 3 months) with first assessment within 2 weeks prior to Cycle 4 treatment. Imaging will include chest and abdomen. Bone Scans and Brain CT/MRI may be performed as clinically indicated. Scans do not have to be repeated once disease progression is documented.

**h:** Adverse events related to fulvestrant and/or everolimus/placebo will be followed for 30 days after the last dose of study therapy (fulvestrant and/or everolimus/placebo) or until ≤ grade 1 or if the grade is >1, the event must be permanent and stable. Please note- Serious adverse events >30 days after last dose of fulvestrant and/or everolimus/placebo are not reported unless the event may be related to everolimus/placebo.

**i:** CBC and chemistry may be used to assess ongoing toxicity but are not required in the Continuation Phase for patients who receive fulvestrant alone. Patients who continue fulvestrant with everolimus should periodically have CBC, chemistries, fasting glucose, fasting lipids, HBV DNA, HCV RNA-PCR per labeling guidelines.

**j:** Study Drug Compliance (Pill Diary) for those patients who receive everolimus in the Continuation Phase.

**k:** All patients including those that discontinue protocol therapy will be followed for 3 years from the time of randomization. Patients that have not progressed during the Induction or Continuation Phase will continue to have imaging scans completed every 12 weeks, +/- 1 week (every 3 months) until documented progression.

**l:** PFTs with DLCO as medically indicated only, (PFTs are not otherwise required during course of study).

**m:** Follow every 3 months for disease progression and survival. Initiation of any new systemic therapy will also be documented.

\* Day 1 of each cycle is defined as the day in which fulvestrant is given, including the first fulvestrant dose, third fulvestrant dose, and every dose thereafter (the second fulvestrant dose is given on day 15 of the first cycle only).

^ End of Induction/End of Treatment should be performed within 30 days of last dose of fulvestrant.

**f:** Continuation Phase: Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) or in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule (+/- 1 week window for scheduled therapy/tests/visits; delays due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted) until disease progression or unacceptable toxicity.

### 13. APPENDIX 3: DISEASE PARAMETERS AND METHODS FOR EVALUATION OF MEASURABLE DISEASE

*The following text is from Protocol Section 6.1.2 and 6.1.3.*

Measurable lesions: are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement) are to be recorded with a minimum size of:

- $\geq 20$  mm by chest x-ray (if clearly defined and surrounded by aerated lung)
- $\geq 10$  mm with CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- $\geq 10$  mm with calipers by clinical exam when superficial

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

Note: Tumor lesions that are situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis (perpendicular to longest diameter) when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions: all other lesions (or sites of disease), including small lesions (longest diameter  $<10$  mm or pathological lymph nodes with  $\geq 10$  to  $<15$  mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses/organomegaly (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability noted above. Blastic bone lesions are non-measurable.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before randomization.

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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a 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 and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when

biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**Tumor markers:** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.<sup>56-58</sup> In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.<sup>59</sup>

**Cytology, Histology:** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

**FDG-PET:** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

## 14. APPENDIX 4: RESPONSE CRITERIA

*The following text is from Protocol Section 6.1.4.1 to 6.1.4.3*

### **Evaluation of Target Lesions**

All measurable lesions up to a maximum of 2 lesions per organ and five lesions in total, 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 (those with the longest diameters), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

**Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

**Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD):** At least a 20% increase in the sum of the diameters 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 over the nadir. (Note: the appearance of one or more new lesions is also considered progression).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease).

### **Evaluation of Non-Target Lesions**

All other lesions or sites of disease including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

### **Evaluation of New Lesions**

The appearance of new lesions constitutes Progressive Disease (PD).

## 15. APPENDIX 5: BEST OVERALL RESPONSE

*The following text is from Protocol Section 6.1.4.4*

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease 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. Note: since response is not the primary endpoint, confirmation is not required.

### Patients with Measurable Disease (e.g., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	Confirmation <u>not required</u>
CR	Non-CR/Non-PD	No	PR	Confirmation <u>not required</u>
CR	Not Evaluated	No	PR	
PR	Non-CR/Non-PD/Not Evaluated	No	PR	
SD	Non-CR/Non-PD/Not Evaluated	No	SD	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

\*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

\*\*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of treatment.

**Patients with Non-Measurable Disease (e.g., Non-Target Disease)**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not Evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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