A Multicenter, Open-label, Single-arm, Study of Enzalutamide Re-Treatment in Metastatic Castration-Resistant Prostate Cancer, As First Treatment Post-Chemotherapy in Patients who Have Previously Received Enzalutamide in the Pre-Chemotherapy Setting

ISN/Protocol 9785-MA-1008

Final Version 1.0, dated 08-July-2015

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Sponsor: Astellas Scientific and Medical Affairs (ASMA)

1 Astellas Way

Northbrook, IL 60062

STATISTICAL ANALYSIS PLAN

Final Version 1.0, dated 08-Jul-2015

Multicenter, open-label, single-arm, study of Enzalutamide Re-Treatment in Metastatic Castration-Resistant Prostate Cancer, As First Treatment Post-Docetaxel in Patients who Have Previously Received Enzalutamide in the Pre-Chemotherapy

ISN: 9785-MA-1008
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Astellas Scientific and Medical Affairs (ASMA)
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Northbrook, IL 60062

Table of Contents

I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
IEC	Independent Ethics Committee
IGF	Insulin-like Growth Factor 1
IL6	Interleukin 6
IL8	Interleukin 8
INR	International Normalized Ratio
IRB	Institutional Review Board
ISN	International Study Number
JAK/STAT	Janus Kinase / Signal Transducer and Activator of Transcription
LA-CRF	Liver Abnormality Case Report Form
LBD	Ligand Binding Domain
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LVEF	Left Ventricular Ejection Fraction
mCRPC	Metastatic Castration- Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	Milligram/Deciliter
mmHg	Millimeters of Mercury
mmol/L	Millimoles/Liter
MOA	Mechanism of Action
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Target of Rapamycin
MUGA	Multiple Gated Acquisition
NASH	Non-alcoholic Steatohepatitis
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
Ng	Nanogram
nmol/L	Nanomole/Liter
NYHA	New York Heart Association
OS	Overall Survival
PCWG2	Prostate Cancer Clinical Trials Working Group
PGAS	Pharmacogenomic Analysis Set
PHI	Protected Health Information
PK	Pharmacokinetics
PSA	Prostate-Specific Antigen
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	Radiographic Progression-Free Survival
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TBL	Total Bilirubin
TLF	Tables, Listings and Figures
sTNF1	Soluble Tumor Necrosis Factor Receptor – 1
TNF-alpha	Tumor Necrosis Factor - Alpha

Abbreviations	Description of abbreviations
TMF	Trial Master File
μL	Microliter
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

List of Key Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol for study 9785-MA-1008, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to database hard lock, or accumulation of substantial amount of data in an open-label study to ensure lack of bias. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician of APGD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

Study Day	**Screening Visit**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**Safety F/U**	**Unscheduled Visit[a]**	**Long-term F/U**
Week	**-4 to -1 (28 days)**	**1**	**5**	**9**	**13**	**17**	**21**	**25 and every subsequent 12 weeks**	**30 days after last dose[b]**	**n/a**	**Every 12 weeks**
Window (days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**n/a**	**± 7**
Informed Consent	X										
Medical History	X										
Inclusion/Exclusion Criteria	X	X									
Vital Signs[c]	X	X[c]	X[c]	X[c]	X	X	X	X	X	X	
Physical Examination, Weight[d]	X[e]	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X										
MUGA/Echocardiogram[f]	X										
Clinical Labs[g]	X	X[h]			X			X	X	X	
PSA[i]	X	X		X	X	X	X	X	X		
CT/MRI and Bone Scan[j]	X			X		X		X			
CXR or Chest CT	X										
ECOG PS	X	X			X			X	X	X	
Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing		X	X	X	X	X	X	X			
Long-Term F/U Assessments[l]											X
Study Drug Treatment[m]		X	X	X	X	X	X	X			
Blood Samples for CTCs and molecular profiling[n]	X				X						
Serum Samples[n]	X				X						

a Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request or if deemed necessary by the investigator.

b Or before the initiation of another systemic antineoplastic therapy, whichever comes first. AE and clinical lab assessment will be performed on the safety follow-up visit, regardless of initiation of another antineoplastic therapy prior to last dose of enzalutamide.

c Vital signs (blood pressure, heart rate, temperature) are to be obtained prior to, and 1–2 hours after the administration of study drug for the first 3 visits.

d A brief physical examination is required at each study visit, with the exception of the Screening visit during which a complete physical examination will be completed.

e Collect weight at this visit only.

f A MUGA scan or echocardiogram is required if the patient has a history of anthracycline treatment, or if the subject has congestive heart failure New York Heart Association (NYHA) class 3 or 4.

g Laboratory assessments include serum chemistries and hematology.

h Collect a blood sample for additional safety testing if indicated.

i PSA progression, defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir, needs to be confirmed by a second consecutive value obtained 3 or more weeks later.

j The window for all radiological assessments is ± 7 days. At Weeks 9, 17, 25 and subsequent assessments prior to treatment discontinuation, all other procedures must be completed within the ± 3 day window. Bone progression at the first reassessment at Week 9 requires a confirmatory scan 6 or more weeks later.

k Adverse events, serious or non-serious, will be collected from the time the patient signs the consent form until the Safety Follow-Up visit, regardless of initiation of another anti-neoplastic therapy prior to last dose of enzalutamide.

l Long-term follow-up for radiographic progressions (until progression or initiation of new anti-neoplastic therapy), survival, and subsequent anticancer therapies should be performed every 12 weeks for a maximum of 3 years from first dose. The study will end when the last subject has been followed for 1 year from date of first dose.

m Enzalutamide will be administered until the disease progression, including radiographic progression or unequivocal clinical progression. Per the Investigator's clinical judgment and with sponsor approval, patients may be allowed to continue enzalutamide until the next treatment is initiated. If another non-cytotoxic, non-investigational, antineoplastic agent is initiated after protocol-defined progression has been determined, enzalutamide may be continued per the Investigator's clinical judgment and with sponsor approval as long as the patient is tolerating enzalutamide and continues androgen deprivation therapy

n Blood samples for CTC molecular profiling and serum samples will be collected at baseline, week 13, time of PSA progression, and time of radiographic progression.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

3.1.1 Primary Objectives

The primary objective is to determine radiographic progression-free survival (rPFS) of re-treatment with enzalutamide + GnRH analogue

3.1.2 Secondary Objectives

The secondary objectives are:

- Assess additional measures of efficacy:
  - Overall survival rate at 1 year
  - Time to PSA progression
  - PSA response rate [maximum decline of ≥30%, ≥50%, and ≥90% from baseline, (PSA30, PSA50, and PSA90), respectively]
  - Objective response rate
- Time to first use of a subsequent antineoplastic therapy
- Assess safety of enzalutamide re-treatment in the post-chemo setting
- Assess correlative science in the post-chemo setting

3.2 Study Design

This is a US-based, multicenter, open-label, single-arm, study evaluating the efficacy, safety, and tolerability of open-label enzalutamide in the re-treatment setting. A total of 40 patients will be enrolled. Patients must have been previously treated with enzalutamide in the pre-chemotherapy setting for a minimum of 8 months, followed by docetaxel for a minimum of 6 cycles. Exposure to intervening systemic anti-cancer therapies such as abiraterone prior to docetaxel is allowed. Subjects will receive treatment with open-label enzalutamide (160 mg daily), administered as four 40 mg capsules, by mouth, once daily, until radiographic or clinical progression (such as pathological fracture, cord compression, worsened pain requiring radiation therapy, or opioid analgesic dose increase or initiation), or unacceptable toxicity. Per the Investigator's clinical judgment and with sponsor approval, patients may be allowed to continue enzalutamide until the next treatment is initiated. If another non-cytotoxic, non-investigational, antineoplastic agent is initiated after protocol-defined progression has been determined, enzalutamide may be continued per the Investigator's clinical judgment and with sponsor approval as long as the patient is tolerating enzalutamide and continues androgen deprivation therapy.

The consensus guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) will be utilized to determine radiographic disease progression. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease. Bone disease progression is considered when a minimum of two new lesions are observed. Progression on bone scan at time points prior to or at week 9 requires a confirmatory scan performed six or more weeks later. This confirmatory

scan should demonstrate at least 2 additional new lesions compared to the Week 9 scan (PCWG2).

The following assessments of prostate cancer status will be collected during the course of the trial: soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, and PSA.

Throughout the study safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs, physical examinations, and safety laboratory evaluations.

Subjects will have a safety follow-up visit approximately 30 days following the last dose of study drug or prior to the initiation of a subsequent anti-cancer drug or investigational agent, whichever occurs first. Survival will be followed every 12 weeks for a maximum of 3 years from first dose. The study will end when the last subject has been followed for 1 year from date of first dose.

Further details of the efficacy assessments can be found in the following sections of the protocol:

1) CT/MRI (imaging) Section 5.3.1
2) PSA Section 5.3.2
3) Correlative samples (biomarker) Section 5.3.3
4) Survival follow-up Section 5.3.4

3.3 Randomization

Not applicable to this study.

4 SAMPLE SIZE

Prior clinical trials data in the post-chemo setting have shown the following median rPFS for subject randomized to initial placebo, placebo+prednisone, or mitoxantrone+prednisone therapy:

- AFFIRM: Placebo = 2.9 months
- COU-301: Placebo + Prednisone = 3.6 months
- TROPIC: Mitoxantrone + Prednisone = 1.4 months

With a sample size of 40 subjects and an assumed median rPFS of 4 months for the therapy defined in this single-arm study, approximately 34 events are expected over a 12-month accrual and 12-month minimum follow-up. Further assuming uniform accrual, 10% loss to follow-up, and an exponential distribution for the rPFS event times, the expected lower bound of the 90% confidence interval for the median is approximately 2.5 months based upon simulations.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock.

5.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who are enrolled in this study, receive at least one dose of study drug, and have at least one post baseline evaluation. This will be the primary analysis set for efficacy analyses.

5.2 Per Protocol Set (PPS)

Not applicable to this study.

5.3 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who took at least one dose of study medication.

The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

5.4 Biomarker Analysis Set (BAS)

The Biomarker analysis set (BAS) consists of the subset of the FAS population for which biomarker data are available to facilitate derivation of at least one of the correlative biomarkers. The Total N used in summaries and analyses for each unique biomarker will be the number of subjects with data available for that unique biomarker.

6 ANALYSIS VARIABLES

The primary efficacy endpoint is:

- Radiographic progression-free survival (rPFS).

The secondary endpoints are:

- additional measures of efficacy:
  - Overall survival rate at 1 year
  - Time to PSA progression
  - PSA response rate [maximum decline of ≥30%, ≥50%, and ≥90% from baseline, (PSA30, PSA50, and PSA90), respectively]
  - Objective response rate

- Time to first use of a subsequent antineoplastic therapy
- Safety of enzalutamide re-treatment in the post-chemo setting

Other efficacy endpoints:

- Composite PFS (cPFS), defined as the earliest date of either radiologic progression, clinical progression, or death

The exploratory endpoints are:

- Correlative science in the post-chemo setting.

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is radiographic progression-free survival (rPFS), which is defined as time from first dose to the radiological progression event or death.

The radiological PFS event is either radiological disease progression defined by either soft tissue tumor progression defined by RECIST 1.1, or the bone progression defined by the Prostate Cancer Clinical Trials Working Group 2 (PCWG2). The bone progression per PCWG2 is defined as a minimum of two new lesions are observed. Progression on bone scan at time points prior to or at Week 9 requires a confirmatory scan performed six or more weeks later. This confirmatory scan should demonstrate at least 2 additional new lesions (PCWG2) compared to the week 9 scan.

rPFS will be censored in the following scenarios:

- If patient has neither PD nor death, the PFS will be censored at last radiological tumor assessment date.
- If patient had PD or Death occurred more 24 weeks (168 days) after previous tumor radiological assessment. The PFS will be censored at last radiological tumor assessment date.
- If patient does not have post baseline tumor assessment, nor death within 24 weeks (168) after first dose, the PFS will be censored at Day 1.
- If patient took any new anti-cancer therapy before any PD event, the PFS will be censored at the last radiological tumor assessment date prior to the date of new anti-cancer therapy.

6.1.2 Secondary Efficacy Endpoints

Time to PSA Progression

For patients with PSA declines, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 μg/L (2 ng/mL) above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later.

For patients with no PSA declines, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 μg/L (2 ng/mL) above the baseline is documented, which is confirmed by a second consecutive value 3 or more weeks later. Baseline is defined as last PSA measurement prior to first dose.

Time to PSA progression is defined as the PSA progression date minus date of first dose + 1, which will be censored in the following scenarios:

- If patient does not have any PSA progression, it will be censored at last PSA sample date.
- If patient does not have post baseline PSA assessment, it will be censored at Day 1.
- If patient took any new anti-cancer therapy before any PSA event, the time to PSA progression will be censored at the PSA sample date prior to the date of new anti-cancer therapy.

Overall Survival Rate at 1 Year

Overall Survival is defined date of death due to any cause minus date of first dose +1. If a patient has not died, overall survival is censored at the last known alive date.

The last known alive date will be derived based on the maximum of last known alive dates in the survival follow up CRF page,last visit, or last SAE onset date.

Overall survival rate at 1 year is defined as the corresponding Year 1 (Day 365) Kaplan-Meier estimate on survival curve.

Time to first use of a subsequent antineoplastic therapy

Time to first use of a subsequent antineoplastic therapy is defined as date of the first systemic antineoplastic therapy minus first dose date +1. If a patient has not started the antineoplastic therapy, the time to event analysis is censored at the last dose date of study medication.

PSA response

PSA response is defined in below categories:

- PSA30 (maximum decline of $\geq$ 30% decline from baseline at lowest post baseline)
- PSA50 (maximum decline of $\geq$ 50% decline from baseline at lowest post baseline)
- PSA90 (maximum decline of $\geq$ 90% decline from baseline at lowest post baseline)

Objective response rate

Objective Response Rate (ORR) is the proportion of patients whose best overall response is Complete Response (CR) or Partial Response (PR) per RECIST 1.1. Only patients with measurable disease at baseline will be included in the analysis of ORR.

Best Overall Response is derived based on the time point response information on the CRF according to RECIST criteria for both subjects with measureable and non-measureable disease:

- CR
- PRNon Cr/Non Pd
- SD
- NE

The derivation of BOR is implemented using SAS based solely on investigator assessed information across all timepoints. Confirmation of response is not required according to the protocol.

6.1.3 Exploratory Efficacy Endpoints

Samples were collected serially at baseline, week 13, at time of PSA progression, and time of radiographic progression and analyzed at central labs for:

1) Androgen receptor
    a. AR-V7
    b. AR-FL
    c. AR-V7/AR-FL ratio
2) Glucocorticoid receptor
    a. GR-FL
3) AR mutations;
    a. L702H
    b. W741C
    c. F876L
    d. T877A
4) Circulating tumor cell detected
5) Inflammatory biomarkers
    a. IL6
    b. IL8
    c. TNF-α (tumor necrotic factor alpha)
    d. sTNFR1 (soluble TNF receptor-1)
6) Neuroendocrine biomarkers
    a. CgA (chromogranin A)
    b. NSE (neuron specific enolase)
    c. Synaptophysin

Other biomarkers may be identified for analysis and SAP will be amended accordingly prior to database lock.

6.1.4 Other Efficacy Variables

A composite endpoint of time to composite progression free survival (cPFS), defined as the earliest date of either radiologic progression, clinical progression, or death, will be analyzed. Radiologic events will be defined as described in Section 6.1.1. Date of clinical progression is the earliest onset date of any AE determined by investigator to be clinical progression.

cPFS will be censored in the following scenarios:

- If patient has no composite PD event the cPFS will be censored at last visit date.
- If patient took any new systemic anti-cancer therapy before any composite PD event, the cPFS will be censored at the last visit date prior to the date of new anti-cancer therapy.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Clinical laboratory variables (hematology, biochemistry including liver enzymes and total bilirubin, and urinalysis)
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- ECOG PS

TEAE is defined as an adverse event observed after first dose of study medication. All adverse events collected that begin within 7 days after taking the last dose of study drug will also be counted as TEAE. Any AE with missing onset date will be considered as TEAE, unless the year and month are prior to the first dose of study medication.

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

Serious adverse events (SAEs) include adverse events that are flagged as serious by the investigator on eCRF, or upgraded by the Sponsor based on review of the Sponsor's list of Always Serious term.

The adverse events will be coded by body system using a MedDRA® dictionary. The severity of adverse event will be graded by NCI CTCAE Grade.

6.3 Pharmacokinetic Variables

Not applicable.

6.4 Pharmacodynamic Variables

Not applicable.

6.5 Other Variables

- The duration of exposure
  For each subject, the duration of exposure will be calculated in days, using the following formula:

  ('Date last dose of study drug'[#] - 'Date first dose[*]) + 1

- Dose Intensity
  Dose Intensity will be examined for subjects in the safety population whose total capsule count is known. Number of capsules which should have been taken depends on the number of days between the date of last and first capsule taken, including both daytimes (further details are given in the Tables Manual):

[Total number of capsules consumed by subject]
---------- x 100
[Total number of capsules subject should have taken]

Where, total number of capsules consumed will be calculated as:
(total number of capsules dispensed) – (total number of capsules returned).

Where total number of capsules should have taken will be calculated by duration of exposure times 4.

Previous and concomitant medication

Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g., 10%, 25%, 75% and 90%) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e., will add up to 100%.

All data processing, summarization, and analyses will be performed using SAS® Version 9.1.3 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

For the definition of subgroups of interest please refer to Section 7.8.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects with informed consent, discontinued before first dose of study medication;
- Number and percentage of subjects in each analysis set;
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation;
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation;

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all dosed patients. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics that have been collected on the eCRF will be summarized by descriptive statistics.

Number and percentage of subjects randomized in each country and site will be presented.

Descriptive statistics for:

Baseline and demographic characteristics:

1) Age (Informed consent date- DOB+1)/365.25
2) Race
3) Ethnicity
4) Screening ECG
5) Weight

6) ECOG Status
7) Measureable disease (y/n)
8) Number of bone lesions at screening
9) Disease sites at screening

Disease History;

1) Time from initial diagnosis to informed consent date (Informed consent date- Initial dx date+1)/365.25
2) Primary Gleason score at initial diagnosis
3) Secondary Gleason score at initial diagnosis
4) Total Gleason score at initial diagnosis
5) PSA result at initial diagnosis
6) Primary tumor assessment at initial diagnosis
7) Pathologic tumor stage at initial diagnosis
8) Clinical lymph node stage at initial diagnosis
9) Pathological lymph node stage at initial diagnosis
10) Distant metastasis at initial diagnosis
11) Anatomic staging at initial diagnosis
12) Time from CRPC diagnosis to informed consent date (Informed consent date- CRPC dx date+1)/365.25
13) CRPC diagnosis criteria
14) Time from initial diagnosis of metastasis to informed consent date (Informed consent date- Metastasis dx date+1)/365.25

Prior Radiation:

1) Prior radiation therapy (y/n)
2) Type of prior radiation therapy
3) Area radiated

Prior Procedures:

1) Any prior procedures (y/n)
2) Type of prior procedures

This will be done for FAS.

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone (in descending order) for the FAS.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF.

As with previous medication, concomitant medication will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for the SAF:

- Descriptive statistics for cumulative amount of the drug subject was exposed to and average daily dose; and
- Number and percent of subject with dose increases, decreases or interruptions.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented.
- Exposure time will be categorized according to the following categories:
    - less than or equal to 28 days
    - greater than 28 days, less than or equal to 84 days
    - greater than 84 days, less than or equal to 168 days
    - Greater than 168 days
    - Unknown.

Counts and percentages of subjects in each of these categories will be summarized for each for the SAF.

Counts and percentages of dose reductions, dose interruptions, and dose discontinuations will be presented.

7.3.2 Treatment Compliance

Overall compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented.
- Percent compliance will be categorized according to the following categories:

- less than 80%
- greater than or equal to 80% and less or equal to 120%
- greater than 120%

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint(s)

The primary analysis will be performed on the Radiographic progression-free survival (rPFS). rPFS will be summarized using descriptive statistics. The survival curve and the median will be estimated using the Kaplan-Meier method. A two-sided 90% confidence interval will be provided for these estimates by use of the Brookmeyer and Crowley method and will be reported along with the corresponding 90% CI.

The SAS code used to produce median from Kaplan-Meier estimates and corresponding 90% CI will be similar to that shown below:

```
proc lifetest data=adtte plots=(s) outsurv=surv;
time survtime*censor(0);
run;
```

An analysis of the primary endpoint will be conducted by subgroups.

7.4.2 Analysis of Secondary Endpoints

Overall Survival, time to PSA progression, and time to first use of a subsequent antineoplastic therapy will be analyzed in the same manner as the primary endpoint.

PSA response rate (PSA30, PSA50, and PSA90) and objective response rate along with exact 90% confidence interval (Clopper-Pearson) will be calculated.

7.4.3 Analysis of Exploratory Endpoints

Unless otherwise noted, all continuous biomarker values will be summarized after log base 2 transformation. Descriptive statistics (e.g., N, mean, standard deviation, minimum, median, maximum for continuous variables; or N, frequency, and percentage for categorical variables) will be provided for baseline blood and plasma samples and by each post-baseline scheduled time point for the following endpoints;

1. AR-V7 (positive/negative status, continuous log base 2 for positive status only)
2. AR-V7 status change from baseline during the study (unchanged, positive to negative, negative to positive)
3. AR-V12/v567es (positive/negative status, continuous log base 2 forpositive status only)
4. AR-V7 positive or AR-V12 positive (yes/no)
5. AR-FL (continuous log base 2)
6. Ratio of (log base 2 AR-V7)/(log base 2 AR-FL) (for positive status AR-V7)

7. GR-FL (continuous log base 2)
8. L702H (yes/no, only descriptive statistics)
9. W741C (yes/no, only descriptive statistics)
10. F876L (yes/no, only descriptive statistics)
11. T877A (yes/no, only descriptive statistics)
12. CTC detected (yes/no)
13. IL6 (continuous log base 2)
14. IL8 (continuous log base 2)
15. TNF-α (tumor necrotic factor alpha) (continuous log base 2)
16. sTNF R1 (soluble TNF receptor-1) (continuous log base 2)
17. CgA (chromogranin A) (categorical split TBD, continuous log base 2)
18. NSE (neuron specific enolase) (categorical split TBD, continuous log base 2)
19. Synaptophysin (categorical split TBD, continuous log base 2)

Three baseline binary AR predictors: 1) AR-V7 status; 2) a composite status (yes/no) of either AR-V7 positive or AR/V-12 positive; and 3) CTC status will be assessed individually, as independent variables, to predict rPFS, time to PSA progression, OS, and composite progression free survival (cPFS) using a single variable Cox model.

Multivariable AR Cox models will then be run on the same endpoints:

1) Using log base 2 transformed baseline AR-FL as a covariate in combination with baseline AR-V7 status;
2) Using log base 2 transformed baseline AR-FL as a covariate in combination with baseline composite AR-V7/V12 response;

Four baseline continuous log base 2 transformed inflammatory cytokine predictors: 1) IL6, 2) IL8, 3) TNF-α, and 4) sTNF R1 will be assessed individually, as independent variables, to predict rPFS, time to PSA progression, OS, and composite progression free survival (cPFS) using a single variable Cox model.

Three baseline continuous log base 2 transformed neuroendocrine predictors: 1) CgA, 2) NSE, and 3) synaptophysin will be assessed individually, as independent variables, to predict rPFS, time to PSA progression, OS, and composite progression free survival (cPFS) using a single variable Cox model.

Hazard ratio point estimates, n, standard errors, p-values, and 90% confidence intervals will be displayed in a single table for all the AR, inflammatory cytokine, and neuroendocrine Cox models.

KM plots, medians, and 90% confidence intervals for the binary AR predictors will be presented for rPFS, time to PSA progression, OS and cPFS.

Waterfall plot of maximum reduction in PSA from baseline with AR-v7, AR-v12, and AR mutation status labeled on the plot.

The AR-V7 and the composite AR-V7/V12 composite predictors will be individually assessed as an independent variables to predict PSA30, PSA50, PSA90, and objective response using Fisher's exact test. Note that objective response will be evaluated using subjects that are both BAS and have measureable disease.

Counts, frequencies, differences in frequencies and 90% Clopper-Pearson methodology will be displayed for the binary AR predictors.

Reported p-values for hazard ratios will use Wald (chi-square) test statistics, and p-values for comparing Kaplan-Meier curves will use log-rank (score) test statistics. Breslow method will be used for handling ties.

In the event that additional exploratory analyses are required for the Clinical Study Report, the SAP will be amended accordingly.

7.4.4 Analysis of Other Variables

Not Applicable.

7.5 Analysis of Safety

All analysis of safety will be presented for SAF, unless specified otherwise.

7.5.1 Adverse Events

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized. Summaries will be provided for:

- TEAEs,
- TEAEs by NCI CTCAE grade
- drug related TEAEs,
- serious TEAEs,
- serious TEAE by NCI CTCAE grade
- drug related serious TEAEs,
- drug related serious TEAEs by NCI CTCAE grade
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5.0%, and
- common TEAEs that equal to or exceed a threshold of 5.0 %.

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized in descending frequency.

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by NCI CTCAE grade to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity, then the subject will be counted only once with the worst severity , however, if any of the severity values are missing then the subject will be counted only once with missing severity. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs will be presented in a similar way by severity only.

TEAEs of special interest will be summarized by the number and percentage of subjects with the following AEs: fatigue, fall, hypertension, non-pathological fractures, cognitive/memory impairment, loss of consciousness, neutropenia, and convulsion.

7.5.2 Clinical Laboratory Evaluation

Quantitative clinical laboratory variables, i.e., hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Baseline is defined as the last available measurement prior to the first study drug dose.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented at each visit.

Laboratory results will also be graded using NCI-CTCAE, where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same subject can be counted for both values if the subject has different laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of subjects for each visit. Shift

tables of lab parameters NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented.

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT, AST, Total Bilirubin	≥ 2xULN
	≥ 3xULN
	≥ 5xULN
ALT or AST	≥ 2xULN
	≥ 3xULN
	≥ 5xULN
ALT and/or AST	(ALT and/or AST ≥ 3xULN) and total bilirubin ≥ 2xULN
And Total Bilirubin(*)	

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver function tests during the investigational period will be presented.

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the investigational period will be presented.

7.5.3 Vital Signs

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs (systolic blood pressure, diastolic blood pressure, ECG parameters (collected only at baseline/screening), and pulse rate) will be summarized using mean, standard deviation, minimum, maximum and median by visit. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized.

Tables for potentially clinically significant vital signs will be generated using baseline value for each subject for each treatment group.

The following potentially clinically significant criteria are defined for each parameter:

Vital Sign Variable	Criteria
SBP	≥180 mmHg AND ≥20 mmHg change from baseline
DBP	≥105 mmHg AND ≥15 mmHg change from baseline
Pulse Rate	≥120 bpm AND ≥15 bpm change from baseline

7.5.4 Electrocardiograms (ECGs)

No post baseline ECG is collected. Not applicable.

7.5.5 Pregnancies

Not applicable.

7.5.6 Other Safety-Related Observations

ECOG PS will be summarized by counts and frequencies by visit

7.6 Analysis of PK

Not applicable.

7.7 Analysis of PD

Not applicable.

7.8 Subgroups of Interest

rPFS, time to PSA progression, and PSA30 will be analyzed for the subgroups defined on the basis of the categorized variables at baseline listed below:

- Ensure to capture subgroups from AFFIRM, plus the following groups of interest to this study
- CTC detected (yes vs no)
- AR-v7 (yes vs no)
- Prior abiraterone
- PSA90 on prior enzalutamide
- Prior enzalutamide treatment duration > median
- PSA50 on prior docetaxel
- Prior docetaxel treatment duration >= median

7.9 Other Analyses

Not applicable.

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

An interim efficacy analysis with no adjustments will be conducted using a cutoff date corresponding to the week 13 visit of 40th subject to report internally on PSA response rates for internal review.

7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Refer to the data specification document in which more details are provided.

7.11.1 Missing Data

As a general principle, no imputation of missing data for other variables will be done. Exceptions are the start and stop dates of AEs and concomitant medication. If day is missing from any date in a derivation then calculate the derived value using 15th day of month. If month or year is missing from any date in a derivation then set the derived value to missing.

Adverse events with missing relationship will be summarized as 'Related to Study Drug'. Adverse events with missing severity grade will be handled as 'missing'.

Incomplete onset dates default AEs to treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

Cases where the onset date of an AE is (partially) missing, will be addressed prior to or during the DRM in order to determine whether the AE must be considered treatment emergent or not.

Imputation on missing date of initial diagnosis (cancer duration) and cancer treatment history (start date, stop date, or date of procedure) will be done as follows:

- Incomplete Day: use the 15th day of the month
- Incomplete Month: use 1st of July if the Year is before Year of dosing, otherwise missing.
- Incomplete Year: no imputation, the derived variable is considered to be missing.

Imputation methods will not be used to determine other endpoints.

Listings will always show the original date information without imputation, but derived parameters (TEAE indicator, start day, end day, study day) will be flagged.

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 Visit Windows

Not applicable.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	DD-MMM-YYYY	NA	Document finalized
2.00	DD-MMM-YYYY	Additional ECG analysis added	Added due to protocol amendment 1.0
		Additional subgroup added	Recent publications suggest relevance of XXX subgroup for safety analysis

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). U.S. Department of Health and Human Service, FDA. Rockvill, MD.

Statistical Review and Evaluation of Xtandi (enzalutamide) on Metastatic Castration-resistant prostat cancer in patients have have previously received docetaxel.

CDER, FDA May 21, 2012

10 APPENDICES

10.1 Appendix 1: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

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