STATISTICAL ANALYSIS PLAN

Version 3.0, dated 23-Mar-2017

A Phase 2, Multicenter, Open-label Study to Assess the Efficacy and Safety of Enzalutamide with Trastuzumab in Subjects with HER2+ AR+ Metastatic or Locally Advanced Breast Cancer

ISN/Protocol: 9785-CL-1121
EudraCT number: 2013-000093-29
IND number: 113,339

Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way,
Northbrook, IL 60062

Table of Contents

I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
AR	Androgen receptor
AUC	Area under the concentration curve
BOR	Best overall response
BORR	Best overall response rate
CBR	Clinical Benefit Rate
CI	Confidence Interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
C_{trough}	Trough concentration
DHT	Dihydrotestosterone
DOR	Duration of response
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
ER	Estrogen receptor
FAS	Full Analysis Set
GD	Global Development
FSH	Follicle stimulating hormone
HER2 or HER2/neu	Human epidermal growth factor receptor 2
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
IRT	Interactive response technology
ISN	International Study Number
LH	Luteinizing hormone
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition scan
N/A	Not applicable
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
OPT	Optional
ORR	Overall response rate
PD	Pharmacodynamic or progressive disease
PDAS	Pharmacodynamic analysis set

Abbreviations	Description of abbreviations
PFS	Progression free survival
PgR	Progesterone Receptor
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	Partial response
PT	Preferred term
RECIST	Response evaluation criteria in solid tumors
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SHBG	Sex hormone binding globulin
SOC	System organ class
TEAE	Treatment emergent adverse event
TLF	Tables listings figures
TTP	Time to Progression
TTR	Time to Response
UNSCH	Unscheduled
W	Week
WHO	World health organization

List of Key Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison. For this study, unless otherwise specified, Baseline finding are the findings observed just prior to the first dose of study drug (enzalutamide or trastuzumab).
Enroll	To enter into a clinical trial in order to begin treatment. Informed consent precedes enrollment.
Screening	Process for checking the eligibility of subjects usually done during the Screening Period and prior to Enrollment.
Screen failure	Subject that was screened but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive study treatment, or decided not to participate anymore (withdrew consent) prior to completing pre-investigational period.
Study drug	Agents given as part of the clinical trial. In this study, enzalutamide and trastuzumab are study drugs.
Study period	Period of time beginning with the first subject consented through to the last observation collected for the study.
Variable	Any quantity, 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, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

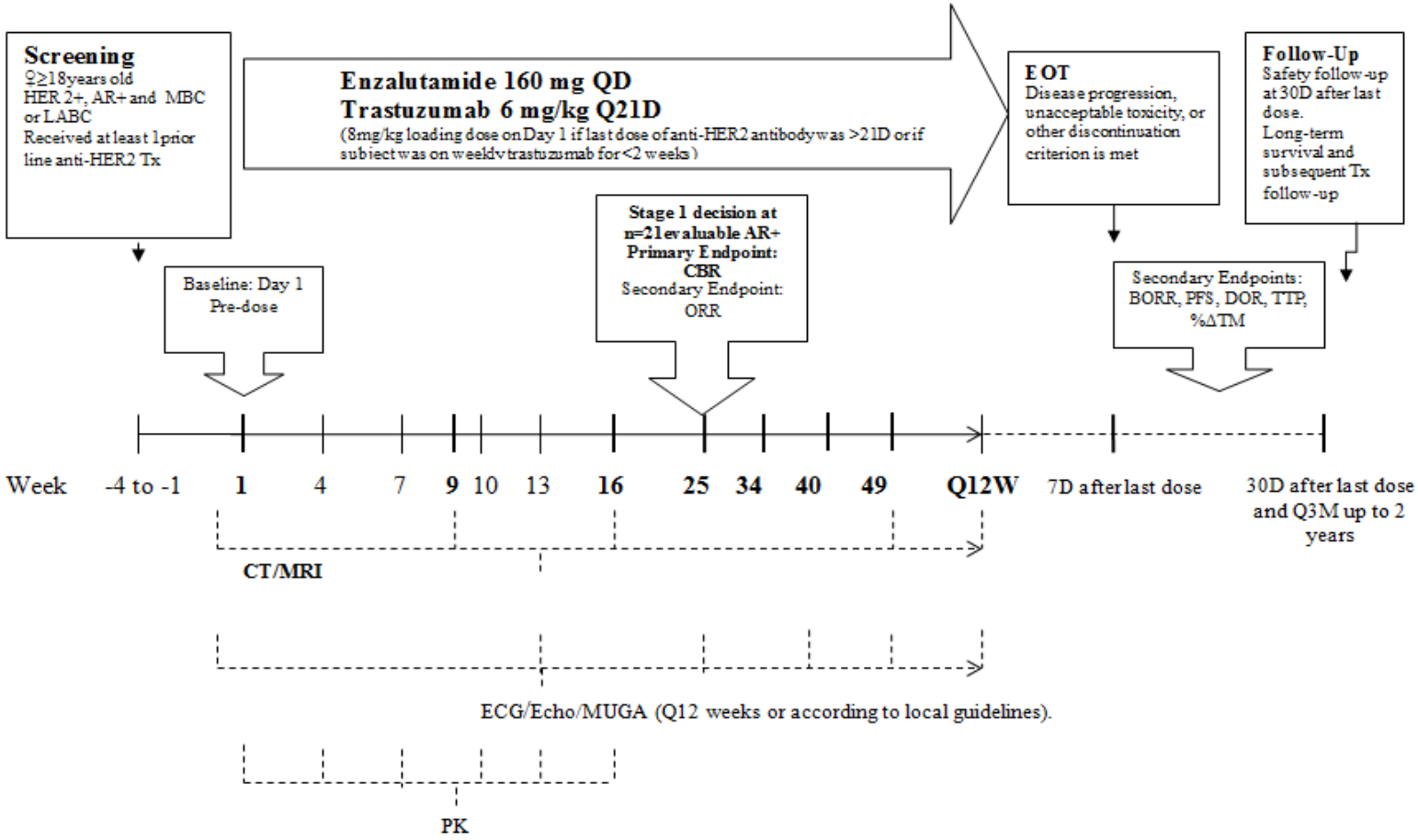
SAP will be drafted before first subject enrolled and finalized before the database soft lock. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician from Data Science. 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

Flow Chart



AR+ = androgen receptor positive, BORR = best overall response rate, CBR = clinical benefit rate, CT = computed tomography, CTx = chemotherapy, D = day, DOR = duration of response, Echo = echocardiogram, EOT = end of treatment, HER2+ = human epithelial growth factor receptor positive, LABC = locally advanced breast cancer, M = month, MBC = metastatic breast cancer, MRI = magnetic resonance imaging, MUGA = multi-gated acquisition scan, ORR = overall response rate, PFS = progression free survival, PK = pharmacokinetics, Q = every, TTP = time to progression, Tx = treatment, W = week, %ΔTM = percent change in tumor measurements.

Assessments	**Prescreen**	**Screen**	**Treatment**											**Follow-up**	
Study Week/Visit	**Prior to screen**	**-4 to -1**	**1**	**4**	**7**	**10**	**13**	**16**	**25**	**34**	**40**	**49 and Q12W**	**UNSCH**	**EOT**	**30D FU[1]**
Study Day	**N/A**	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	**169**	**232**	**274**	**337+**	**N/A**	**≤ 7D after last dose**	**30D after last dose**
Window (days)	**N/A**	**N/A**	**0**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**N/A**	**N/A**	**+7**
Informed Consent	X	X													
Initial AR expression testing[2]	X														
Inclusion/Exclusion Criteria		X	X												
Return and/or Dispense Enzalutamide			X	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Trastuzumab administration			To be administered Q3W												
Concomitant Medications[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Demographics, Medical and Disease History		X													
Radiographic Disease Assessment[4]		X	To be performed Q8W (+/- 10 D)									X	X [OPT]		
Brain Imaging[5]		X											X [OPT]		
Height		X													
Weight		X	X				X		X	X	X	X	X [OPT]	X	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Adverse Events[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests[7]		X[8]	X[9]	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Urine Pregnancy Test[10]		X	X		X		X	X	X	X	X	X	X [OPT]	X	X
Physical Examination[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[12]		X	To be performed Q12W (+/- 14D) or according to local guidelines										X [OPT]	X	
Echocardiogram/MUGA/MPS		X	To be performed Q12W (+/- 14D) or according to local guidelines										X [OPT]		
ECOG PS		X	X	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Circulating Endocrine and Other Protein Markers[13]			X	X	X	X	X	X	X	X	X	X		X	
PK Samples[14]			X	X	X	X	X	X					X [OPT]		
Dosing Diary Review[15]			X	X	X	X	X	X							
Tumor Tissue Collection for Central Testing[16]		X													
Blood Sample for Genotype Analysis[17]			X												
Optional PGx Sample[18]			X												

Footnotes appear on next page

1. Phone call may be conducted only if subject is unable to return to the clinic. Follow-up visit should occur approximately 30 days following the last dose of study drug, or before initiation of subsequent treatment (whichever is first). Subjects who discontinue treatment for a reason other than disease progression will continue to have tumor assessment performed according to the protocol schedule until progression, initiation of new therapy, or withdrawal of consent
2. Testing of archival tissue for AR expression can be done before initiation of other screening activities under a separate pre-screen consent form. Results for AR expression from local pathology can be used for enrollment.
3. Medications taken within 14 days before the Screening visit and up to 30 Day-Follow-up visit will be collected.
4. CT/MRI of the chest/abdomen/pelvis as well as any other anatomical region appropriate for that subject's disease must be performed within 28 days prior to day 1. Results from CT/MRI assessments performed prior to consent and within 28 days of day 1 may be used for screening if available. All patients should have a bone imaging assess metastasis to the bone within 6 months prior to the Day 1 visit. Thereafter, subjects without bone metastasis will have bone scans only if clinically indicated. PR and CR require confirmation with equivalent or improved assessment no less than 4 weeks after the date of scan that PR or CR was first observed.
5. Brain imaging is required at Screening for all subjects to rule out central nervous system disease.A brain MRI with contrast enhancement is required unless it cannot be performed within 2 weeks prior to Day 1due to feasibility or subject-specific contraindications. A head CT may be performed in these situations after discussion with the medical monitor or designee.
6. Adverse Events will be collected from the time of informed consent through 30 days following last dose of study drug or through the day prior to initiation of alternate treatment (whichever occurs first).
7. Clinical Laboratory Assessments include hematology, chemistry, and local urine dipstick. Coagulation panel will be performed at Screening for all subjects and only at each visit if subject is on anti-coagulant therapy.
8. Local FSH testing is required at screening for postmenopausal women who are < 55 years of age.
9. Day 1 clinical laboratory tests do not need to be repeated if Screening labs were performed within 7 days prior to Day 1.
10. Urine pregnancy test will be performed in women of child-bearing potential. Testing at treatment visits must occur prior to study drug administration.
11. Physical exam performed prior to ICF and within 7 days of the screening visit may be used for screening if available.
12. All on-treatment ECGs will be obtained prior to drug administration. In addition, whenever a study procedure coincides with the scheduled time point for an ECG, the study activities should be undertaken in a fixed sequence if possible: ECGs first, vital signs second, and any type of blood draw as the last assessment.
13. Blood samples to measure circulating endocrine levels and other protein markers will be obtained. Blood sample should be obtained prior to study drug administration at the Day 1 visit and at approximately the same time of day at each following visit.
14. Pre-dose plasma PK samples will be collected prior to enzalutamide intake and will be analyzed for enzalutamide and N-desmethyl enzalutamide. Pre-dose serum PK samples will be collected prior to the start of the trastuzumab infusion and will be analyzed for trastuzumab. Enzalutamide and trastuzumab will be administered in clinic on PK days.
15. A dosing diary will be dispensed to the subject on Day 1. Date and time of enzalutamide dose will be recorded in the diary by the subject for the 2 days prior to each PK sample.
16. All subjects are required to have tissue sample available to send for central lab confirmation of AR expression at screening visit.
17. A blood sample is taken to allow evaluation of potential AR mutations and another sample is taken to allow for genotype analysis of relevant metabolism, transporter, PD, and/or safety genes, in the event of unusual PK/PD patterns or safety findings.
18. Optional exploratory retrospective, PGx for those subjects who consent to the sub-study.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

3.1.1 Primary Objective

To evaluate the efficacy of enzalutamide with trastuzumab in evaluable subjects with human epidermal growth factor receptor 2 positive (HER2+), androgen receptor positive (AR+), metastatic or locally advanced breast cancer, as measured by Clinical Benefit Rate (CBR24), defined as the proportion of evaluable subjects with best objective response of confirmed CR or PR per RECIST 1.1, or prolonged SD (≥ 24 weeks).

3.1.2 Secondary Objectives

- To evaluate the following efficacy measures:
  - Best Overall Response Rate (BORR)
  - Overall Response Rate (ORR) at 24 weeks
  - Progression Free Survival (PFS)
  - Time to Progression (TTP)
  - Duration of Response (DOR)
  - Time to Response (TTR)
- To evaluate the safety and tolerability.

3.1.3 Exploratory Objectives

- [redacted]

3.2 Study Design

This is a multinational, multicenter, open-label, single-arm, two-stage, Phase 2 study evaluating the efficacy, safety, and tolerability of enzalutamide with trastuzumab. The study population includes female subjects with HER2+, AR+, metastatic or locally advanced breast cancer who have progressed on at least 1 prior line of anti-HER2 therapy in the metastatic or advanced setting. Subjects may be either ER/PgR positive or negative according to the local assessment for hormone receptor diagnostic. A line of therapy is defined as a course of treatment at the end of which there was disease progression, toxicity, or in the investigator's opinion, maximum benefit has been achieved. Approximately 50 centers in North America and Europe will conduct the study. Approximately 80 subjects will be enrolled to reach 66 evaluable AR+ subjects.

A Simon's two-stage design is implemented to allow for early termination if < 3 of 21 evaluable AR+ subjects show clinical benefit [confirmed complete response (CR), partial

response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, criteria or prolonged stable disease (SD) ≥ 24 weeks] at the analysis of the first stage. If ≥ 3 of 21 evaluable AR+ subjects show clinical benefit, then a second stage will continue to enroll a total of 66 evaluable AR+ subjects.

Subjects will enter the screening period up to 28 days prior to treatment start. Subjects will be allowed to pre-screen under a separate consent form to enable testing of archival tissue for AR expression before initiation of other screening activities. After completion of screening assessments, eligible subjects will enter into the treatment phase to receive enzalutamide with trastuzumab. Study visits will take place every 3 weeks until week 16, then at weeks 25, 34, 40, and 49, and then every 12 weeks thereafter until the subject meets discontinuation criteria or the study ends. Tumor assessments will be performed every 8 weeks through week 49, and then every 12 weeks thereafter. Subjects will continue on treatment until disease progression, unacceptable toxicity, or any other discontinuation criteria are met. Subjects who discontinue study drug for a reason other than disease progression will continue to have tumor assessments performed, when possible, according to the protocol schedule until disease progression, initiation of new therapy, or withdrawal of consent. Upon discontinuation of study drug, subjects will enter the follow-up period. An end of treatment visit will be performed within 7 days of the last dose of enzalutamide. The Follow-up Visit will be performed 30 days after the last dose of enzalutamide or before initiation of subsequent treatment (whichever occurs first); this visit may be conducted by phone call if the subject is unable to return to the clinic. The treatment emergent period will be defined as the period of time from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment (whichever occurs first). All adverse events that occur during the collection period are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If the study is terminated early for reasons other than safety, and the subject is receiving clinical benefit per investigator judgment, the subject may continue on study medication until they have disease progression as defined per RECIST.

3.3 Randomization

This is a single arm study. All subjects will receive the same treatment. An Interactive Response Technology (IRT) system will be used to register subjects and to assign specific enzalutamide containers by packaging lot to subjects. Specific procedures for the IRT are contained in a separate IRT procedures manual.

4 SAMPLE SIZE

The sample size is sufficient to determine the absence or presence of an efficacy signal. The sample sizes for the first and second stage were determined using optimal Simon's two-stage design. The null hypothesis that the true CBR is 10% will be tested against a one-sided alternative at a 5% significance level. In the first stage, 21 evaluable subjects will be evaluated; the study will stop if < 3 evaluable subjects show CR, PR, or SD ≥ 24 weeks.

Otherwise, the study will continue to enroll up to 66 evaluable subjects. This design has a statistical power of 90% when the true CBR is 25% (East version 5.4, Cytel Inc). To illustrate the precision with a total of 66 subjects: if the observed CBR is 40%, then the 90% confidence interval will be within the 30% to 50% range.

Taking into account the number of non-evaluable subjects, approximately 80 subjects will be enrolled to get 66 evaluable subjects.

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.

For the determination of the percentage tumor cells with nuclear expression, the Ventana assay will be used.

5.1 All Enrolled Subjects (AES)

The All Enrolled Subjects (AES) consists of all subjects who are found to be eligible for treatment and enrolled using the IRT at the Day 1 visit.

5.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all enrolled subjects who have centrally assessed AR+ breast cancer (defined as $\geq$10% of tumor cells with nuclear expression), and received at least one dose of study drug.

5.3 Efficacy Evaluable Set (EES)

The Efficacy Evaluable Set (EES) is a subset of the FAS defined as all enrolled subjects who have centrally assessed AR+ breast cancer (defined as $\geq$10% of tumor cells with nuclear expression), received at least one dose of study drug, and have at least one available post baseline tumor assessment.

The selection of subjects for the FAS and EES will be confirmed in the Analysis Set Classification Meeting (ASCM).

The primary analyses will be done on the EES, while all efficacy analyses will be done on both the EES and FAS.

5.4 Low AR Expression Set (LARES)

In the event that more than 5 subjects have a central assessment of AR+ expression less than 10%, an additional analysis set will be defined for the primary efficacy end-point.

The Low AR Expression Set (LARES) consists of enrolled subjects who received at least one dose of study drug, and had central assessment of AR+ expression <10%.

5.5 Per Protocol Set (PPS)

PPS is not defined for this study and separate analyses will not be performed on a PPS.

5.6 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all subjects who have received at least 1 or partial dose of study drug.

The SAF will be used for the statistical summary of the safety data.

5.7 Pharmacokinetics Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF population for which at least one quantifiable enzalutamide, N-desmethyl enzalutamide, or trastuzumab concentration value is available. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the Classification Specifications.

The PKAS will be used for all tables and graphical summaries of the PK data.

5.8 Pharmacodynamic Analysis Set (PDAS)

The pharmacodynamic analysis set (PDAS) will include the subjects from the SAF population for whom sufficient pharmacodynamic measurements (a baseline and at least one post-baseline sample) were collected. The PDAS will be used for all analyses of pharmacodynamic data.

Any formal definitions for exclusion of subjects from the PDAS will be documented in the Classification Specifications.

The PDAS will be used for all analyses of pharmacodynamic data.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint(s)

The Primary Efficacy Endpoint is Clinical Benefit Rate (CBR). CBR is defined as the proportion of evaluable subjects with best objective response of confirmed CR, PR per RECIST 1.1, or prolonged SD (≥ 24 weeks).

6.1.2 Secondary Efficacy Endpoints

The Secondary Efficacy Endpoints include:

- Overall response rate (CR or PR) according to RECIST 1.1 criteria.
- Best overall response rate according to RECIST 1.1.
- PFS, defined as the time from the date of first dose of enzalutamide until the date of disease progression per RECIST 1.1 or death from any cause on study (death within 168 days after treatment discontinuation), whichever occurs first.

- TTP, defined as the time from the first date of enzalutamide treatment until the date of disease progression per RECIST 1.1.
- DOR, defined as the time from the date of first documentation of response (CR or PR) until the date of disease progression per RECIST 1.1.
- TTR, defined as the time from the first date of enzalutamide treatment to initial CR or PR.

6.1.3 Other Efficacy Variables

Percent change of tumor diameter in target lesions based on the smallest value post-baseline.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; any, CTCAE grade, seriousness, action taken and relationship to study drug).
- Clinical laboratory variables (hematology, biochemistry including liver tests, coagulation parameters and urinalysis)
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- 12-lead electrocardiogram (ECG)
- Left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated acquisition scan (MUGA).

TEAE is defined as an adverse event observed during the treatment emergent period, which is from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment or date of death, whichever is first. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent.

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.

6.3 Exploratory Endpoints

6.3.1 [redacted]

[redacted]

6.3.2 [redacted]

[redacted]

6.3.3 [redacted]

[redacted]

7 STATISTICAL METHODOLOGY

7.1 General Considerations

Prior to database lock, a Final Review of Data and Tables, Listings and Figures (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 lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

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% [Q25], 75% [Q75], 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 9.3 or higher on Unix. Specifications for tables, figures, and data listing formats can be found in the TLF specifications for this study.

7.2 Study Population

7.2.1 Disposition of Subjects

Number and percentage of subjects screened, discontinued before enrollment, and enrolled will be presented for all subjects screened.

The following subject data will be presented for the AES:

- Number and percentage of subjects in each analysis set;
- Number and percentage of subjects discontinued treatment, by primary reason for treatment discontinuation;
- Number and percentage of subjects discontinued study, by primary reason for treatment discontinuation;
- Number and percentage of subjects completed the study.

Number and percentage of subjects enrolled in each country and site will be presented for the All Enrolled Subjects Set.

The duration from date of first intake/administration of study drug to date of permanent treatment discontinuation due to any primary reason will be analyzed by Kaplan-Meier method for SAF. For subjects in whom no event occurs within the reporting period the censoring date will be date of last medication intake. The number of subjects who already experienced a treatment discontinuation due to any reason, the number of subjects still at risk and Kaplan-Meier estimates with two-sided 95% CI of cumulative incidence will be presented at the following time points: Days 22, 43, 64, 85, 106, 169, 232, 274, 337 and thereafter every 84 days as appropriate.

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 7.8 Protocol Deviations) will be assessed for the AES. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall as well as by study site. 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 disease history will be summarized by descriptive statistics for the SAF, FAS, EES and LARES.

For demographics table, descriptive statistics will be presented for age, weight, body mass index (BMI) and height at study entry. Frequency tabulations for ethnicity, age group (≤ 65, 66-75, and >75 yr) and race will be presented. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

For disease history table, descriptive statistics will be presented for time from initial diagnostis. Frequency tabulations will be presented for histopathology at diagnosis, histologic grade, anatomic staging, primary tumor stage, regional lymph node stage (clinical/pathological), distant metastasis, HER2 Status, HER2 testing method confirming HER2 status, ER status, PgR status, AR+ status (Nuclear staining by Ventana), and number of lines of prior therapy. Two scatter plots will be made to access the correlation of the

percentage of AR+ between Ventana and Dako, for 1) Nuclear staining, and 2) cytoplasmic staining.

Prior cancer procedures treatment will be summarized for the SAF.

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, for the SAF.

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

7.3.1.1 Enzalutamide

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

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

Duration of exposure will be summarized in two ways:

- Summary statistics, including quantiles, will be presented for subjects in the SAF.
- Exposure time will be categorized according to the following categories by study drug:
  - less than 3 months
  - at least 3 months and less than 6 months
  - at least 6 months.

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

7.3.1.2 Trastuzumab

Summaries for the following data will be provided for Trastuzumab:

- Number of Infusion Started
- Number of Completed Infusion Administration
- Number of Incomplete Infusion Administration
- Reason for dose interruption/discontinuation.

Summary statistics, including quantiles, will be provided for each of these variables for subjects in the SAF.

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 for Enzalutamide and Trastuzumab will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by study drug.
- Percent compliance will be categorized according to the following categories by study drug:
  - less than 80%
  - at least 80%, less or equal to 90%
  - greater than 90%

  and also as:
  - less than 80%
  - greater or equal than 80%
- Treatment compliance of enzalutamide is defined as:
  (Total amount of study drug actually consumed per subject) / (Amount of study drug that should have been taken [=number of days on study drug x 4 capsules] per subject) * 100
- Treatment compliance of trastuzumab is defined as the percentage of the number of completed infusions per patient over total infusions per patient * 100. Total infusion is the number of completed, incomplete or missed infusion administrations.

7.4 Analysis of Efficacy

The primary analyses will be done in the EES, while all efficacy analyses will be done in both the EES and FAS. If more than 5 subjects are enrolled into the study but had less than 10% of tumor cells with nuclear expression, and received at least one dose of study drug, the efficacy analyses will also be conducted on this analysis set (LARES).

7.4.1 Analysis of Primary Endpoint

The primary efficacy endpoint, CBR, will be presented using descriptive statistics and will be summarized including 95% two-sided exact confidence intervals (CIs). Clopper-Pearson method will be used for exact intervals.

The primary analysis will be done on the EES. Same analysis will also be done on FAS, and on LARES (analysis set with AR+ less than 10%, if more than 5 subjects enrolled, took at least one dose of study medication, and had central assessment of AR expression <10%). Analysis will also be done on the data from the combined FAS and LARES.

7.4.2 Analysis of Secondary Endpoints

All variables will be presented as descriptive statistics. ORR, and BORR will be summarized including 95% two-sided exact CIs (Clopper Pearson Method). Kaplan-Meier curves will be

calculated to estimate the median (95% CI), Q25 and Q75 times for duration (DOR), progression free times (PFS), and times to Progression (TTP) and to Response (TTR).

7.4.2.1 Overall Response Rate

Overall response rate (CR or PR) is defined according to RECIST 1.1 criteria.

7.4.2.2 Best Overall Response Rate

Best overall response rate is defined according to RECIST 1.1. Two sets of analysis will be conducted: one with confirmed PR/CR, and one without confirmation. Sponsor-derived Best Overall Response (BOR) will be used in the analysis. If there is a discrepancy between the investigator rated BOR and sponsor-derived BOR, a sensitivity analysis will be done using investigator rated BOR. Both derived and investigator rated BOR will be presented in listing.

7.4.2.3 Progression-Free Survival

PFS is defined as the time from the date of first dose of enzalutamide until the date of disease progression per RECIST 1.1, or death from any cause on study (death within 168 days after treatment discontinuation), whichever occurs first. For analysis data will be used up to and including the cut-off date. The following subjects will be censored at the date of the last radiological assessment showing no progression: 1) subjects who initiated another anti-tumor therapy before documented PD or death, 2) subjects who progressed or died after missing two or more consecutive radiological assessments. Subjects are considered to have missed two or more consecutive radiological assessments if duration between two consecutive imaging scans are more than 20 weeks while on treatment or more than 30 weeks off-treatment. Subjects who have no valid post-baseline tumor assessment will be censored at first dose of enzalutamide.

A sensitivity analysis will be done with the rule listed above, except that initiation of another anti-tumor therapy will be considered as an event.

7.4.2.4 Time to Progression

TTP is defined as the time from the first date of enzalutamide treatment until the date of disease progression per RECIST 1.1. The following subjects will be censored at the date of the last radiological assessment showing no progression: 1) subjects who initiated another anti-tumor therapy before documented PD; 2) subjects who progressed after missing two or more consecutive radiological assessments; 3) subjects who died before disease progression. Subjects are considered to have missed two or more consecutive radiological assessments if duration between two consecutive imaging scans are more than 20 weeks while on treatment or more than 30 weeks off-treatment. Subjects who have no valid post-baseline tumor assessment will be censored at first dose of enzalutamide.

7.4.2.5 Duration of Response

DOR is defined as the time from the date of first documentation of response (CR or PR) until the date of disease progression per RECIST 1.1. DOR is defined for subjects who achieved

BOR of CR or PR only. The following subjects will be censored at the date of the last radiological assessment showing no progression: 1) subjects who initiated another anti-tumor therapy before documented PD; 2) subjects who progressed after missing two or more consecutive radiological assessments; 3) subjects who died before disease progression. Subjects are considered to have missed two or more consecutive radiological assessments if duration between two consecutive imaging scans are more than 20 weeks while on treatment or more than 30 weeks off-treatment. Subjects who have no valid post-baseline tumor assessment will be censored at first dose of enzalutamide.

For subjects with confirmed CR or confirmed PR, duration of response will be analyzed using Kaplan-Meier estimates, and the median with corresponding two-sided 95% CI will also be reported.

7.4.2.6 Time to Response

TTR is defined as the time from the first date of enzalutamide treatment to initial CR or PR.

For subjects with a confirmed CR or confirmed PR, simple descriptive statistics will be presented.

7.4.3 Analysis of Exploratory Endpoints

Waterfall plot will be done for percent change of tumor diameter in target lesions.

7.4.3.1 [redacted]

[redacted]

n

[redacted]

7.4.3.2 [redacted]

[redacted]

7.4.3.3 [redacted]

[redacted]

7.5 Analysis of Safety

Safety will be assessed on an ongoing basis by physical examination, measurement of vital signs, laboratory assessments, 12-lead ECGs, left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated acquisition scan (MUGA), and evaluation of adverse events/serious adverse events.

Safety analyses will be conducted using the SAF and restricted to the treatment emergent period. The SAF is defined as all subjects who have initiated at least 1 or partial dose of study drug. The treatment emergent period will be defined as the period of time from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment (whichever is first). Only data within this period will be summarized in safety analysis. Safety will be assessed through descriptive statistics for the frequency of adverse events by system organ class (SOC), preferred term (PT), and NCI CTCAE grade, the frequency of treatment discontinuations due to adverse events, vital signs, ECG, LVEF, and laboratory evaluations.

7.5.1 Adverse Events

The severity of all adverse events is to be evaluated by the Investigator based on the NCI CTCAE, version 4.03. All adverse events will be coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects with treatment emergent adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and NCI CTCAE grade. A subject reporting the same adverse event more than

once is counted once and at the maximum severity or strongest relationship to study drug treatment, when calculating incidence.

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by SOC and PT.

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 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,
- Number of drug related TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with drug related TEAEs leading to permanent discontinuation of study drug,
- Number of deaths,
- Number and percentage of subjects with TEAEs leading to dose reduction,
- Number and percentage of subjects with TEAEs leading to interruption.

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

- TEAEs,
- Drug related TEAEs,
- Grade 3 or higher TEAEs.
- Serious TEAEs,
- Drug related serious TEAEs,
- TEAEs leading to dose reduction of enzalutamide,
- Drug related TEAEs leading to dose reduction enzalutamide,
- TEAEs leading to permanent discontinuation of study drug,
- Drug related TEAEs leading to permanent discontinuation of study drug,
- Common TEAEs that equal to or exceed a threshold of 5% of the subjects,
- TEAEs of interest.

TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by grade and by relationship to study drug. If an adverse event changes in grade or relationship, then the subject will be counted only once with the maximum grade and highest degree of relationship. The adverse event however will be presented in each category they were classified to. If a subject has an event more than once

with missing grade/relationship and with non-missing grade/relationship, then the subject will be counted as missing. Drug related TEAEs will be presented in a similar way by grade only.

The Always Serious Terms (AST) List is a list of AEs that a Sponsor determines regardless of Investigator assessment are to be captured as serious. Serious TEAEs table will include both investigator reported and Astellas upgraded ones according to AST list. In the listing they will be presented with different flag.

The number and percentage of subjects with treatment-emergent adverse events of interest, as classified by SOC and PT will also be summarized. The list of adverse events of interest to be summarized may change during the course of the study due to ongoing pharmacovigilance. It will be finalized before the database hard lock.

7.5.2 Clinical Laboratory Evaluation

For selected quantitative laboratory parameter, summary statistics of change from baseline value by visit will be presented. The baseline laboratory value is defined as the last laboratory value collected on or prior to the first dose date of enzalutamide or trastuzumab.

Using the definitions provided in the NCI-CTCAE Version 4.03, lab values will be classified as Grade 1 through 4, where possible. For each lab parameter at each scheduled collection time point, the number and percentage of subjects who have lab values within the categories defined by each of the grades will be displayed. If a subject has multiple lab values that fall into more than one NCI-CTCAE grade, the highest NCI-CTCAE grade will be displayed for that subject. In the event the NCI-CTCAE grade is listed as > ULN or < LLN, the normal ranges of local labs will be used for the purposes of comparison. These values are maintained by the Data Management group using the New England Journal of Medicine SI Unit Conversion Guide as a reference.

Shift tables will be created for each of the lab parameters after classifying by NCI-CTCAE criteria. Shift from baseline to the highest NCI-CTCAE grade will be presented. Shift tables for high and low abnormalities will be summarized separately.

Grade 3 and higher lab abnormalities will also be summarized by number and percent, by visit and overall during the study.

7.5.2.1 Liver Tests

The number and percentage of subjects with potentially clinically significant values in liver tests will be presented. A drug induced liver injury (DILI) table will also be generated.

7.5.3 Vital Signs

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

The number and proportion of subjects experiencing potentially clinically significant abnormalities during the treatment-emergent period will be summarized. The definitions of potentially clinically significant abnormalities are provided in the table below.

Parameter	Criteria for Potentially Clinically Significant Abnormalities
Systolic blood pressure	Absolute result > 180 mm Hg and increase from baseline > 40 mm Hg
	Absolute result < 90 mm Hg and decrease from baseline > 30 mm Hg
	Final visit or 2 consecutive visits results ≥ 20 mm Hg change from baseline
	Most extreme post baseline result ≥ 140 mm Hg
	Most extreme post baseline result ≥ 180 mm Hg
	Most extreme result ≥ 180 mm Hg and ≥ 20 mm Hg change from baseline
	Most extreme result ≥ 140 mm Hg and ≥ 20 mm Hg change from baseline
Diastolic blood pressure	Absolute result > 105 mm Hg and increase from baseline >30 mm Hg
	Absolute result < 50 mm Hg and decrease from baseline >20 mm Hg
	Final visit or 2 consecutive visits results ≥ 15 mm Hg change from baseline
	Most extreme post-baseline result ≥ 90 mm Hg
	Most extreme post-baseline result ≥ 105 mm Hg
	Most extreme result ≥ 105 mm Hg and ≥ 15 mm Hg change from baseline
	Most extreme result ≥ 90 mm Hg and ≥ 15 mm Hg change from baseline
Pulse Rate	Absolute result >120 bpm and increase from baseline >30 bpm
	Absolute result < 50 bpm and decrease from baseline >20 bpm

bpm, beats per minute; mm Hg, millimeters of mercury.

7.5.4 Electrocardiograms (ECGs)

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results for the 12-lead ECG will be tabulated by visit.

The QTc interval will be summarized using frequency tables for each time point for values of clinical importance using the range criteria below.

	QTc Interval Criteria Values
Normal	≤ 450 msec
Borderline	> 450 and ≤ 480 msec
Prolonged	> 480 and ≤ 500 msec
Clinically significant	> 500 msec

QT data using Fredericia's (QTcF) and Bazett's (QTcB) correction will be used for the categorization:

- QTcF: QT interval corrected for heart rate using Fridericia's formula = $QT/\sqrt[3]{RR}$.
- QTcB: QT interval corrected for heart rate using Bazett's formula = $QT/\sqrt[2]{RR}$

Note: for the calculations the value of RR should be in seconds (not milliseconds).

The QTc interval (QTcF and QTcB) will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each time point.

Variable	Change from Baseline
QTc Interval (msec)	<0 msec ≥ 0 and ≤ 30 msec > 30 and ≤ 60 msec > 60 msec

7.5.5 Pregnancies

A detailed listing of all pregnancies will be provided.

7.5.6 Other Safety-Related Observations

7.5.6.1 Physical Examination

All clinically significant abnormal findings will be recorded as baseline conditions or adverse events and graded using NCI-CTCAE guidelines. There will be no separate summary report for physical exams. Instead, any findings from physical exams will be summarized and reported as part of baseline conditions or adverse events.

7.5.6.2 LVEF

Descriptive statistics will be used to summarize LVEF data and changes from baseline data by time point.

7.5.6.3 ECOG

Descriptive statistics will be used to summarize ECOG data and changes from baseline data by time point.

7.6 Analysis of PK

Pharmacokinetic analyses will be conducted using the PKAS.

The enzalutamide, N-desmethyl enzalutamide, and trastuzumab concentration-time data will be summarized by descriptive statistics at each visit. Additional model-based analyses may be performed and will be described in a separate population PK analysis plan.

7.7 Analysis of PD

7.7.1 Pharmacodynamic Analyses

Circulating hormones and protein markers will be expressed as the change in absolute value and percent change from baseline at each visit and presented using descriptive statistics.

Additional model-based analyses to explore PK-PD relationships may be performed and will be described in separate PK analysis plan.

7.8 Subgroups of Interest

Subgroup analysis will be done on the primary endpoint based on number of lines of prior therapy (1-2, 3-4 or >4) in the metastatic or locally advanced disease setting, and ER/PgR status of the subjects. The latter implies that the subgroup analysis will be done on:

- Subjects with negative ER status *and* negative PgR status, and
- Subjects positive ER *and/or* positive PgR status.

Analyses will be done on the EES.

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

Recruitment will continue if there are 3 or more subjects with clinical benefit in the first 21 evaluable subjects from the evaluable set. If there are less than three subjects who demonstrate CBR, recruitment will be stopped.

Tumor response will be monitored continuously throughout Stage 1, therefore it is expected that the decision to expand enrollment using the CBR after 24 weeks will be made before the 21st subject is evaluated.

Once the 21st evaluable subject reaches week 24, a data cut will be applied for stage one data. Planned efficacy and safety analysis will be done on stage 1 data for EES, FAS, and SAF.

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

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment period, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

7.10.1 Missing Data

Subjects who do not satisfy the criteria to be counted as responders or have insufficient data to determine or confirm a response per the RECIST 1.1 Criteria will be considered as non-responders in the primary final analysis of response rates. No imputation of data will be done to determine individual subject response.

For continuous variables (e.g., clinical laboratory measurement, vital signs), subjects with missing baseline variable will be excluded from the analysis of change from baseline.

Missing end of treatment information will be imputed by last observation carried forward, if applicable. Visit-by-visit analyses of data will exclude subjects who did not provide data at the visit in question. Missing ECOG performance status at end of treatmentwill be imputed by last observation carried forward, unless the subject is known to have died (Grade 5). For visit by visit summary of ECOG, no imputation will be made.

The imputed dates will be used to allocate the relative study day of the concomitant medication and AEs to treatment, in addition to determining whether an AE is/is not treatment emergent. Imputation on missing non-prostate cancer related concomitant medication dates (to categorize them as previous medications or concomitant medications) and adverse event dates (to categorize them as TEAE or not) will be done as follows:

- Incomplete Start Day: use the later of (first day of the month, first dosing day if first dosing month)

Imputation on missing date of initial diagnosis (cancer duration) and cancer treatment history, including prior prostate cancer drug therapies, (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

For all analyses other than PK analysis, all values will be included in the analyses. For analysis of PK data, only samples for which the time of sampling relative to the dose and the exact dose is known will be included.

7.10.2 Outliers

All values will be included in the analyses.

7.10.3 Visit Windows

Analyses will not exclude any subject's data due to the subject's failure to comply with the visit schedule. Labs, vital signs, weight, ECOG, ECG, and LVEF will be analyzed based on the following visit window.

Visit (study day)	Lab, Vital signs, ECOG	Weight	ECG, LVEF
Baseline (1)	<= 1	<= 1	<= 1
Week 4 (22)	>=2 – <33	NA	NA
Week 7 (43)	>=33 – < 54	NA	NA
Week 10 (64)	>=54 – <75	NA	NA
Week 13 (85)	>=75 – <96	>=2 – < 128	>=2 – <128
Week 16 (106)	>=96 – <138	NA	NA
Week 25 (169)	>=138 – < 201	>=128 – <201	>=128 – < 210
Week 34 (232)	>=201 – <254	>=201 – <254	NA
Week 37 (253)	NA	NA	>= 210 – <292
Week 40 (274)	>=254 – <310	>=254 – <306	NA
Week 49 (337)	>=310 – <380	>=306 - <380	>=292 – <380
Week 61 (421)	>=380 – <468	>=380 – <468	>=380 – <468
Week 73 (505)	>=468 – <554	>=468 – <554	>=468 – <554
Week 85 (589)	>=554 – <640	>=554 – <640	>=554 – <640
Q12W…	If data available at Day 640 or later, then adapt table accordingly.		

If more than 1 assessment occurs within a given visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the earlier assessment will be used.

8 DOCUMENT REVISION HISTORY

Version	Change
1.1	Update changes from protocol amendment 4.
2.0	Update changes from protocol amendment 5., making SAP consistent with the statistical analysis conducted for the same study in TNBc studies (MDV3100-11)
	Removal of the OS as an endpoint Clarification in the summary of treatment compliance and exposure for enzalutamide and trastuzumab Added summary for adverse events of interests Clarification in time to response analysis Additional AE summaries Clarification in windowing algorithm
3.0	Added two abbreviations (CI, and ICF) to List of Abbreviations Section 4: Added "optimal" before "Simon's two-stage design"in first sentence Section 5: Added"for clarification ""For the determination of the percentage tumor cells with nuclear expression, the Ventana assay will be used." Added Section 5.4 Low AR Expression Set (LARES) Section 6.1.2 & 7.4.2.1: Overall Response Rate: deleted "at 24 weeks", CR or PR instead of CR+PR Section 6.1.2: Ädded "(death within 168 days after treatment discontinuation) Section 7.1 Deleted "Summaries based on FAS and EES (e.g. baseline and efficacy data) will be presented, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented." Section 7.2.1: Text regarding treatment discontinuation and Kaplan-Meier updated Section 7.2.3: Deleted in 3rd paragraph "This will be done for the SAF, FAS and EES populations." Section 7.2.3; version number of MedDRA deleted Section 7.2.4: Text "Prior cancer procedures treatment will also be summarized for the SAF."moved to Section 7.2.3. Section 7.3.1.1: 1st bullet, text updated after "Duration of exposure will be summarized in two ways" Section 7.3.2: 2nd bullet, changed -80% to 80%. 3rd bullet, format updated 3rd bullet: added "[=number of days on study drug x 4 capsules]" Section 7.4: last sentence "in this subset of FAS" replaced by "on this analysis set (LARES)" Section 7.4.1: second paragraph, "subset" replace by analysis set" Added text: Analysis will also be done on the data from the combined FAS and LARES Text on subgroup analysis deleted Section 7.4.2: 2nd sentence, added (Clopper Pearson Method). Text regarding Kaplan Meier method rewritten Section 7.4.2.3: Added after the first sentence: For analysis data will be used up to and including the cut-off date Section 7.4.3: Added text Section 7.5.1: Added "TEAEs leading to" to the text related to dose reduction and interruption. Section 7.5.1: CTCAE instead of CTC Section 7.5.2:1 Liver Tests instead of Liver Function Tests Section 7.5.3: In table "Heart rate" replaced by "Pulse rate"

Version	Change
	Section 7.5.4: Text regarding QTc interval inserted Section 7.5.6.2 & 7.5.6.3: text adapted Section 7.7.2.1: Added Section on Biomarker Analyses Section 7.8: subgroup analysis for ER-/PgR- subjects is specified. Added: "Analyses will be done on the EES." Section 7.10.1: changed study into treatment in sentence describing missing ECOG performance status. 3rd paragraph end of treatment instead of end of study Section 7.10.3: replaced MUFA by LVEF Extended the "window visit" table. Deleted "PE" from sentence above table and from 2nd column header of the table

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)

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al.: New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (Version 1.1). Eur J Cancer. 2009; 45(2):228-247.

10 APPENDICES

10.1 Appendix 1: Definition of Progression-Free Survival

Progression free survival (PFS) is defined as the time interval from the date of the first dose of enzalutamide to the date of disease progression as determined by the investigator using RECIST 1.1 or the date of on-study death due to any cause, whichever occurs first. Patients who die after receiving the first dose of enzalutamide without post baseline tumor assessments evaluable using RECIST 1.1, will be considered to have a PFS event on the date of death. The censoring rules for the primary and sensitivity analyses of PFS are summarized in the following table. The earliest of the following censoring times will be used:

Analysis	Censoring Rules	Date of Censoring
Primary analysis of PFS	Patients with no post baseline assessments	Date of first dose of enzalutamide +1
	Patients who had no disease progression per RECIST 1.1 or died before data cutoff date	Date of the last tumor assessment before data cutoff date
	Patients who had no disease progression per RECIST 1.1 died before initiating use of a new antitumor treatment	Date of the last tumor assessment before use of a new antitumor treatment
	Patients who had no disease progression per RECIST 1.1 before treatment discontinuation for reason ‘lost to follow-up’	Date of the last available tumor assessment when patient was known to be progression free
Sensitivity PFS	Patients who discontinued study treatment for disease progression not by RECIST 1.1 (e.g. end of trial)	This is an EVENT (not censoring) occurring at the date of treatment discontinuation
	Patients who received a new antitumor treatment (antineoplastic or investigational therapy) without documented disease progression per RECIST 1.1	This is an EVENT (not censoring) occurring at the date of initiation of the new antitumor treatment.

10.2 Appendix 2: Signatures

Prepared by: _____ Date: _____
[redacted], MSc. Date (DD Mmm YYYY)

Approved by: _____ Date: _____
[redacted], M.S. Date (DD Mmm YYYY)

Reviewed by: _____ Date: _____
[redacted], M.D. Date (DD Mmm YYYY)

_____ _____
[redacted], CCRP Date (DD Mmm YYYY)