Clinical trial results:
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

Summary

EudraCT number	2013-000093-29
Trial protocol	BE GB ES IT
Global end of trial date	30 January 2024

Results information

Result version number	v1 (current)
This version publication date	22 December 2024
First version publication date	22 December 2024

Trial information

Trial identification

Sponsor protocol code	9785-CL-1121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02091960
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical transparency, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical transparency, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of enzalutamide with trastuzumab in evaluable participants with human epidermal growth factor receptor 2 positive (HER2+) and androgen receptor positive (AR+) metastatic or locally advanced breast cancer, as measured by Clinical Benefit Rate (CBR).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	103
EEA total number of subjects	32

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 35 clinical sites in Belgium, Canada, Italy, Spain, the United Kingdom and the United States.

Pre-assignment

Screening details:

This study enrolled women with HER2+ and AR+ metastatic or locally advanced breast cancer who progressed on anti-HER2 therapy in the metastatic or advanced setting.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Enzalutamide + Trastuzumab

Arm description:

Participants received 160 (milligrams) mg enzalutamide orally once daily and 6 mg/kg trastuzumab administered by intravenous infusion or subcutaneous injection every 21 days. Participants continued on treatment until disease progression, unacceptable toxicity or any other discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Participants received 6 mg/kg trastuzumab intravenously/subcutaneously once every 21 days.

Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 160 mg enzalutamide orally once daily.

Number of subjects in period 1	Enzalutamide + Trastuzumab
Started	103
Completed	58
Not completed	45
Adverse event, serious fatal	7
Consent withdrawn by subject	1
Miscelleneous	37

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide + Trastuzumab
Reporting group description:	
Participants received 160 (milligrams) mg enzalutamide orally once daily and 6 mg/kg trastuzumab administered by intravenous infusion or subcutaneous injection every 21 days. Participants continued on treatment until disease progression, unacceptable toxicity or any other discontinuation criteria were met.	

Reporting group values	Enzalutamide + Trastuzumab	Total	
Number of subjects	103	103	
Age Categorical Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	75	75	
From 65-84 years	28	28	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	59.3		
standard deviation	± 10.0	-	
Gender Categorical Units: Participants			
Female	103	103	
Male	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	98	98	
Race/Ethnicity, Customized Units: Subjects			
White	90	90	
Black or African American	8	8	
Asian	3	3	
American Indian or Alaskan Native	0	0	
Native Hawaiian or other Pacific Islander	1	1	
Other	1	1	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self care, unable to carry out any			

work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	51	51	
Grade 1	51	51	
Missing	1	1	
Histopathology at Diagnosis Units: Subjects			
Ductal	73	73	
Inflammatory	5	5	
Intraductal	6	6	
Lobular	6	6	
Mixed	1	1	
Not otherwise specified	1	1	
Other	5	5	
Unknown	6	6	
Anatomic Stage			
Breast cancer staging is based on size of the tumor, whether cancer cells have spread to lymph nodes or to other parts of the body, how aggressive the cells appear when viewed under a microscope, whether the cancer cells have receptors for estrogen and progesterone or have a gene mutation that causes them to make excess HER2 protein, and the results of gene expression profiling tests. The stages of breast cancer range from 0 to IV, where Stage 0 is noninvasive or contained within the milk ducts and Stage IV breast cancer, also called metastatic, has spread to other areas of the body.			
Units: Subjects			
Stage 0	3	3	
Stage IA	6	6	
Stage IB	1	1	
Stage IIA	14	14	
Stage IIB	12	12	
Stage IIIA	5	5	
Stage IIIB	7	7	
Stage IIIC	7	7	
Stage IV	28	28	
Unknown	20	20	
Time from Initial Diagnosis of Primary Cancer to Enrollment			
Number of participants analyzed = 95			
Units: days			
median	1199		
full range (min-max)	30 to 4713	-	

End points

End points reporting groups

Reporting group title	Enzalutamide + Trastuzumab

Reporting group description:

Participants received 160 (milligrams) mg enzalutamide orally once daily and 6 mg/kg trastuzumab administered by intravenous infusion or subcutaneous injection every 21 days. Participants continued on treatment until disease progression, unacceptable toxicity or any other discontinuation criteria were met.

Subject analysis set title	Efficacy Evaluable Set (EES)
Subject analysis set type	Per protocol

Subject analysis set description:

The EES was a subset of the FAS (Full analysis set) defined as all enrolled participants who had centrally assessed AR+ breast cancer (defined as >10% of tumor cells with nuclear expression), received at least one dose of study drug, and had at least one available post baseline tumor assessment.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of all participants who had received at least 1 or partial dose of study drug.

Primary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)[1]

End point description:

CBR was defined as percentage of evaluable participants with best objective response of confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or prolonged stable disease (≥ 24 weeks). CR was defined as the disappearance of all target and non-target lesions and no new lesions, and lymph nodes all < 10 mm in short axis. PR was defined as disappearance of target lesions or a ≥ 30% decrease in the size of target lesions, with persistence of non-target lesions and no new lesions. Stable disease (SD) was defined as < 30% decrease and < 20% increase in size of target lesions, persistence of non-target lesions, and no new lesions. PR and CR required confirmation with equivalent or improved assessment no less than 4 weeks after date that PR or CR was first observed. SD required confirmation with equivalent or improved assessment no less than 8 weeks after enrollment. Participants in EES with available data were analyzed.

End point type	Primary

End point timeframe:

Tumor assessments were performed every 8 weeks through week 49, and then every 12 weeks thereafter until disease progression or death; the median duration of treatment was 70 days, and the maximum was 660 days.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: Percentage of participants				
number (confidence interval 95%)	23.6 (15.2 to 33.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate at Week 24

End point title	Overall Response Rate at Week 24

End point description:

Overall response rate was defined as the percentage of evaluable participants with a best objective response of confirmed complete response (CR) or partial response (PR) per RECIST 1.1. Complete response was defined as the disappearance of all target and non-target lesions and no new lesions, and lymph nodes all < 10 mm in short axis. Partial response was defined as disappearance of target lesions or a ≥ 30% decrease in the size of target lesions with persistence of non-target lesions and no new lesions. PR and CR required confirmation with equivalent or improved assessment no less than 4 weeks after the date of scan that PR or CR was first observed. Participants in the EES population with available data were analyzed.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage of participants				
number (confidence interval 95%)	3.4 (0.7 to 9.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression was defined as the time from the first date of enzalutamide treatment until the date of disease progression per RECIST 1.1. Participants who initiated another anti-tumor therapy before documented PD, who progressed after missing two or more consecutive radiological assessments or who died before disease progression were censored at the date of the last radiological assessment showing no progression. Participants in the EES population with available data were analyzed.

End point type	Secondary

End point timeframe:

From the date of first dose of study drug until disease progression or death; the median duration of treatment was 70 days, and the maximum was 660 days.

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: days				
median (full range (min-max))	108.0 (61 to 116)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate

End point title	Best Overall Response Rate

End point description:

Best overall response was the best response across all time points, based on investigator assessments. Best overall response rate was defined as the percentage of evaluable participants with a best objective response of confirmed complete response (CR) or partial response (PR) at any time during the study per RECIST 1.1. Complete response was defined as the disappearance of all target and non-target lesions and no new lesions, and lymph nodes all < 10 mm in short axis. Partial response was defined as disappearance of target lesions or a ≥ 30% decrease in the size of target lesions with persistence of non-target lesions and no new lesions. PR and CR required confirmation with equivalent or improved assessment no less than 4 weeks after the date of scan that PR or CR was first observed. Participants in the EES population with available data were analyzed.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 8 weeks through week 49, and then every 12 weeks thereafter until disease progression or death; the median duration of treatment was 70 days, and the maximum was 660 days.

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage of participants				
number (confidence interval 95%)	4.5 (1.2 to 11.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival was 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, whichever occurred first. Participants who initiated another antitumor therapy before documented progressive disease (PD) or death, or who progressed or died after missing 2 or more consecutive radiological assessments were

censored at the date of the last radiological assessment showing no progression. Progressive disease was defined as a ≥ 20% increase in the size of target lesions and at least a 5 mm increase in size of target lesions from smallest size on study, or unequivocal progression of non-target lesions, or any new lesions. Participants in the EES population with available data were analyzed.

End point type	Secondary

End point timeframe:

From the date of first dose of study drug until disease progression or death; the median duration of treatment was 70 days, and the maximum was 660 days.

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: days				
median (confidence interval 95%)	105.0 (61 to 116)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was 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. Participants who initiated another anti-tumor therapy before documented PD, progressed after missing two or more consecutive radiological assessments or who died before disease progression were censored at the date of the last radiological assessment showing no progression. Participants in the EES population with best overall response of CR or PR were analyzed. 99999 = the data could not be analyzed due to low number of events.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 8 weeks through week 49, and then every 12 weeks thereafter until disease progression or death; the median duration of treatment was 70 days, and the maximum was 660 days.

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time from the first date of enzalutamide treatment to initial CR or PR and was calculated for participants with a CR or PR. Participants in the EES population with best overall response of CR or PR were analyzed.

End point type	Secondary

End point timeframe:

From the date of first dose of study drug until disease progression or death; the median duration of treatment was 70 days, and the maximum was 660 days.

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: days				
median (confidence interval 95%)	57 (57 to 222)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered study drug/who underwent study procedures and did not necessarily have a causal relationship with treatment. Abnormalities identified during medical tests were defined as an AE if they induced clinical signs/symptoms, required active intervention, interruption or discontinuation of study medication, or were clinically significant to investigator. An AE was defined as serious if any of the following resulted: Death, was life-threatening, persistent or significant disability/incapacity or substantial disruption of ability to conduct normal life functions, congenital anomaly/ birth defect, inpatient hospitalization/prolongation of hospitalization or other medically important event. TEAE was defined as an AE observed during the treatment emergent period, which is from first dose date of study drug to 30 days after last dose date or start of subsequent treatment or date of death, whichever is first. SAF.

End point type	Secondary

End point timeframe:

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 (Up to 3031 days)

End point values	Enzalutamide + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Participants				
Any treatment emergent adverse events (TEAE)	97			
Enzalutamide Related TEAE	75			
Trastuzumab Related TEAE	40			
Any Drug Related TEAE	78			
Deaths	4			
Serious TEAE	24			
Enzalutamide Related Serious TEAE	3			
Trastuzumab Related Serious TEAE	0			
Any Drug Related Serious TEAE	3			
TEAE leading to discontinuation of enzalutamide	23			
TEAE leading to discontinuation of trastuzumab	21			
TEAE leading to discontinuation of any study drug	24			
Discontinuation due to enzalutamide Related TEAE	5			
Discontinuation due to trastuzumab Related TEAE	5			
Discontinuation due to Any Drug Related TEAE	9			
TEAE Leading to Dose Reduction	7			
TEAE Leading to Dose Interruption	23			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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 (Up to 3031 days).

Adverse event reporting additional description:

The Safety Analysis Set (SAF) consisted of all participants who had received at least 1 or partial dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v23.0

Reporting groups

Reporting group title	Enzalutamide + Trastuzumab

Reporting group description:

Participants received 160 mg enzalutamide orally once daily and 6 mg/kg trastuzumab administered by intravenous infusion or subcutaneous injection every 21 days. Participants continued on treatment until disease progression, unacceptable toxicity or any other discontinuation criteria were met.

Serious adverse events	Enzalutamide + Trastuzumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 103 (23.30%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin neoplasm bleeding			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin cancer			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myxoid liposarcoma			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to skin			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	5 / 103 (4.85%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Brain neoplasm malignant			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Accidental overdose			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Embolism				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Asthenia				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Dyspepsia				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	2 / 103 (1.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	3 / 103 (2.91%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			

Vomiting			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	3 / 103 (2.91%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Enzalutamide + Trastuzumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 103 (86.41%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	17 / 103 (16.50%)		
occurrences (all)	18		
Hypertension			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	9		
Nervous system disorders			
Restless legs syndrome			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	7		
Headache			

subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	17 / 103 (16.50%) 19 14 / 103 (13.59%) 16		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 9 / 103 (8.74%) 10		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	 37 / 103 (35.92%) 60 6 / 103 (5.83%) 6		
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 10 / 103 (9.71%) 10 14 / 103 (13.59%) 16 15 / 103 (14.56%) 16 28 / 103 (27.18%) 33 10 / 103 (9.71%) 10		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 15 / 103 (14.56%) 16		

Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 9 / 103 (8.74%) 13 10 / 103 (9.71%) 10		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 6 / 103 (5.83%) 6		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 9 / 103 (8.74%) 12		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 13 / 103 (12.62%) 19 13 / 103 (12.62%) 14 6 / 103 (5.83%) 7 7 / 103 (6.80%) 8 15 / 103 (14.56%) 16 6 / 103 (5.83%) 7		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed occurrences (all)	15 / 103 (14.56%) 16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2014	Changes included: • Updated the primary objective to clarify that CBR is evaluable participants with CR, PR at any point or stable disease ≥ 24 weeks. • Removed OS (long-term follow-up post study drug termination). • Updated timeline for prestudy radiographic bone assessment requirement at 6 mo prior to enrollment (day 1). • Updated prior line requirements to provide clarity regarding prior lines of therapy, the definition of disease progression, and the use of trastuzumab in the adjuvant setting in Inclusion Criterion 7. • Aligned protocol visits with trastuzumab infusion visits. All protocol-required visits are now in increments of 3 weeks (i.e., 6, 9, 12) in order to line-up with the trastuzumab infusion visits conducted every 3 weeks. • Clarified language allowing fresh tissue biopsy to be done only in cases of known local AR+ status per local report but insufficient tissue sample available to send for central confirmation. • Updated pregnancy language to remove hormonal contraceptive agents (oral, injected or implanted hormones) as a possible form of contraception. The pregnancy language was updated per the Astellas standard protocol template. • Updated the duration requirement for contraception and breastfeeding. Inclusion Criterion 12 extended the contraceptive use and breastfeeding restriction requirement from 3 to 6 months after study drug discontinuation.
06 October 2014	Changes also included: • Updated exclusion language to prevent enrollment of patients with potential renal insufficiency. Exclusion Criterion 4 includes creatinine clearance in addition to the creatinine level to restrict entry of patients with renal insufficiency. • Updated trastuzumab dose noted per locally available formulation. Subcutaneous added as available route of administration. • Clarified allowed estrogen use. Vaginal estrogen creams were allowed while on study. • Updated scope of efficacy endpoint. Removed initiation of new antitumor therapy from efficacy endpoint. • Updated pharmacokinetic data in Introduction section. • Updated statistical sections to reflect clarifications made to primary efficacy definition, clarification in various analyses sets and removal of OS. • Added myocardial perfusion scintigraphy (MPS) as allowable procedure for screening and subsequent visits in lieu of an echocardiogram (ECHO) or multigated acquisition (MUGA) scan. • Updated physical examination and added a 7-day window within screening visit for the physical examination to be done prior to signing of the informed consent form. • Removed vital sign requirement that temperature should be measured orally. • Removed the pharmacodynamic blood draw for circulating hormones and protein marker collection at the screening visit.
10 June 2015	Changes included: • Removed requirement for participants to have HER2 positive breast cancer that is ER negative and PgR negative. • Updated Inclusion Criterion 7 to remove the cap on the required number of prior lines of therapy the participants can receive, to clarify the definition of a prior line of therapy, to allow discontinuation of the most recent regimen for any toxicity except cardiotoxicity and to allow nonapproved anti-HER2 agents in the most recent regimen. • Updated Inclusion Criterion 6 to allow participants with non-measurable, evaluable disease per RECIST 1.1 to be eligible for enrollment in the study. In addition, the Schedule of Assessments was modified to clarify when patients with non-measurable, evaluable disease must have efficacy assessments completed. • Updated Inclusion Criterion 7 and Exclusion Criterion 16 to allow patients that had received pertuzumab as the most recent line of therapy. • Updated the protocol text and Inclusion Criterion 10 to change the preferred source of archival tissue from a primary tumor to the most recent biopsy available. • Updated Exclusion Criterion 16 to exclude participants who, in the investigator’s opinion, may benefit from hormonal therapy during the study.
09 August 2018	Changes included: • Removed assessment of circulating endocrine and other protein markers and pharmacokinetic samples. • Updated to include the definition of urgent safety measures and procedures for reporting them.

30 November 2020	Changes included: • The instruction that participants who discontinued study drug for a reason other than disease progression will continue to have tumor assessments performed was removed from the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported