Clinical trial results:
A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase II Study of the Efficacy and Safety of Trastuzumab Emtansine in Combination with Atezolizumab or Atezolizumab-Placebo in Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer who Have Received Prior Trastuzumab and Taxane Based Therapy

Summary

EudraCT number	2015-004189-27
Trial protocol	DE ES GB IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	26 December 2018
First version publication date	26 December 2018

Trial information

Trial identification

Sponsor protocol code	WO30085

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02924883
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	Interim
Date of interim/final analysis	11 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 December 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This Phase II, double-blind, randomized, placebo-controlled multicenter study investigated the efficacy and safety of trastuzumab emtansine in combination with atezolizumab or atezolizumab-placebo in participants with HER2-positive locally advanced or metastatic BC who have received prior trastuzumab and taxane based therapy, either alone or in combination, and/or who have progressed within 6 months after completing adjuvant therapy.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	202
EEA total number of subjects	76

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)	176
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Approximately 200 patients were enrolled and randomized to both treatment arms in a 1:2 ratio.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab Emtansine + Placebo

Arm description:

Placebo matched to atezolizumab followed by trastuzumab emtansine 3.6 mg/kg IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the sponsor (approximately 40 months)

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab Emtansine
Investigational medicinal product code	
Other name	Kadcyla
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab emtansine was administered 3.6 mg/kg IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo (matching to atezolizumab) was administered by IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor.

Arm title	Trastuzumab Emtansine + Atezolizumab

Arm description:

Atezolizumab 1200 milligrams (mg) intravenous (IV) infusion followed by trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor (approximately 40 months)

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

Dosage and administration details:

Trastuzumab emtansine was administered 3.6 mg/kg IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab 1200 mg was administered by IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor.

Number of subjects in period 1	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab
Started	69	133
Completed	56	115
Not completed	13	18
Adverse event, serious fatal	8	13
Consent withdrawn by subject	5	4
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab Emtansine + Placebo
Reporting group description:	
Placebo matched to atezolizumab followed by trastuzumab emtansine 3.6 mg/kg IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the sponsor (approximately 40 months)	
Reporting group title	Trastuzumab Emtansine + Atezolizumab
Reporting group description:	
Atezolizumab 1200 milligrams (mg) intravenous (IV) infusion followed by trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor (approximately 40 months)	

Reporting group values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab	Total
Number of subjects	69	133	202
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	58	118	176
From 65-84 years	11	15	26
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	54.4	53.7	
standard deviation	± 10.9	± 9.9	-
Sex: Female, Male Units: Subjects			
Female	69	131	200
Male	0	2	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	23	49	72
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	1	5	6
White	44	72	116
More than one race	0	1	1
Unknown or Not Reported	1	5	6
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	1	10	11
Not Hispanic or Latino	66	114	180
Unknown or Not Reported	2	9	11

End points

End points reporting groups

Reporting group title	Trastuzumab Emtansine + Placebo
Reporting group description:	
Placebo matched to atezolizumab followed by trastuzumab emtansine 3.6 mg/kg IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the sponsor (approximately 40 months)	
Reporting group title	Trastuzumab Emtansine + Atezolizumab
Reporting group description:	
Atezolizumab 1200 milligrams (mg) intravenous (IV) infusion followed by trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor (approximately 40 months)	

Primary: Progression-Free Survival (PFS) as Determined by Investigator's Tumor Assessment Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1)

End point title	Progression-Free Survival (PFS) as Determined by Investigator's Tumor Assessment Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1)
End point description:	
PFS was defined as the time from randomization to the first occurrence of disease progression or death from any cause, whichever occurred first, on the basis of investigator assessments. Progression was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 millimeter (mm) or the appearance of one or more new lesions.	
End point type	Primary
End point timeframe:	
Baseline up to clinical cut off date (11 Dec 2017)	

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	133		
Units: months				
median (confidence interval 95%)	6.8 (4.0 to 11.1)	8.2 (5.8 to 10.7)		

Statistical analyses

Statistical analysis title	Progression-Free Survival
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Atezolizumab

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3332
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.23

Primary: Percentage of Subjects with Adverse Events

End point title	Percentage of Subjects with Adverse Events[1]

End point description:

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Primary

End point timeframe:

Baseline up to clinical cut off date (11 Dec 2017)

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: There were no statistical analysis done for this endpoint.

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	132		
Units: percentage of subjects				
number (not applicable)	95.6	99.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death from any cause. 9999 = OS event not reached at time of analysis

End point type	Secondary

End point timeframe:

Baseline up to clinical cut off date (11 Dec 2017)

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	133		
Units: Months				
median (confidence interval 95%)	12.9 (12.8 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Atezolizumab
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4577
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.77

Secondary: Percentage of Subjects With Objective Response (OR) as Determined by Investigator's Tumor Assessment Using RECIST v1.1

End point title	Percentage of Subjects With Objective Response (OR) as Determined by Investigator's Tumor Assessment Using RECIST v1.1

End point description:

An OR was defined as a complete or partial response determined on 2 consecutive occasions ≥ 4 weeks apart using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Complete response was defined as the disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must be < 10 mm on the short axis. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum. Participants who had no post-baseline tumor assessment were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline up to clinical cut off date (11 Dec 2017)

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	133		
Units: Percentage of subjects				
number (not applicable)	43.5	45.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of OR as Determined by Investigator's Tumor Assessment Using RECIST v1.1

End point title	Duration of OR as Determined by Investigator's Tumor Assessment Using RECIST v1.1

End point description:

Duration of OR was defined as the time from the first tumor assessment that was judged to indicate that the patient had an objective response to the time of first documented disease progression using RECIST v1.1 per investigator assessment or death from any cause, whichever occurred first. 9999 = Duration of OR was not reached at time of analysis

End point type	Secondary

End point timeframe:

Baseline up to clinical cut off date (11 Dec 2017)

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	133		
Units: Months				
median (confidence interval 95%)	9999 (9.9 to 9999)	9999 (7.1 to 9999)		

Statistical analyses

Statistical analysis title	Duration of Objective Response
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Atezolizumab

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6099
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	3.03

Secondary: Steady State Maximum Serum Concentration (Cmax) of Trastuzumab Emtansine

End point title	Steady State Maximum Serum Concentration (Cmax) of Trastuzumab Emtansine[2]

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion (0 hour [h]), 30 minutes (min) after end of infusion (EOI) (over 90 min) on Day 1 Cycles 1 and 4; pre-infusion (0 h) on Day 1 Cycle 2 (each cycle = 21 days); at any time during study treatment/early discontinuation visit (approx. 40 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done for this endpoint.

End point values	Trastuzumab Emtansine + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: ug/mL				
arithmetic mean (standard deviation)	80.9 (± 21.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Steady State Cmax of Deacetyl Mercapto 1-Oxopropyl Maytansine

End point title	Steady State Cmax of Deacetyl Mercapto 1-Oxopropyl Maytansine[3]

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion (0 h) on Day 1 Cycle 1 and 30 min after EOI (over 90 min) on Day 1 Cycles 1 and 4 (each

cycle = 21 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done for this endpoint.

End point values	Trastuzumab Emtansine + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: ng/mL				
arithmetic mean (standard deviation)	5.46 (± 5.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Steady State Cmax of Total Trastuzumab

End point title	Steady State Cmax of Total Trastuzumab[4]

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion (0 h), 30 min after EOI (over 90 min) on Day 1 Cycles 1 and 4; pre-infusion (0 h) on Day 1 Cycle 2 (each cycle = 21 days)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done for this endpoint.

End point values	Trastuzumab Emtansine + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: ug/mL				
arithmetic mean (standard deviation)	93.1 (± 24.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cycle 4 Cmax of Atezolizumab

End point title	Cycle 4 Cmax of Atezolizumab[5]

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion (0 h), 30 min after EOI (over 60 min) on Day 1 Cycles 1 and 4; pre-infusion (0 h) on Day 1 Cycles 2, 3, 8, and every 8 cycles thereafter (each cycle=21 days) up to 120 days after treatment completion/early discontinuation (approx. 40 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done for this endpoint.

End point values	Trastuzumab Emtansine + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: ug/mL				
arithmetic mean (standard deviation)	637 (± 146)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-therapeutic Antibodies (ATAs) to Atezolizumab

End point title	Percentage of Participants With Anti-therapeutic Antibodies (ATAs) to Atezolizumab[6]

End point description:

ATAs are antibodies that inactivate the therapeutic effects of Atezolizumab. Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥ 0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response).

End point type	Secondary

End point timeframe:

Pre-infusion (0 h) on Day 1 Cycles 1, 2, 3, 4, 8, and every 8 cycles thereafter (each cycle = 21 days) up to 120 days after treatment completion or early discontinuation (approximately 40 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done for this endpoint.

End point values	Trastuzumab Emtansine + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Percentage of participants				
number (not applicable)	12.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ATAs to Trastuzumab Emtansine

End point title	Percentage of Participants With ATAs to Trastuzumab Emtansine

End point description:

ATAs are antibodies that inactivate the therapeutic effects of Trastuzumab Emtansine. Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥ 0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response).

End point type	Secondary

End point timeframe:

Pre-infusion (0 h) on Day 1 Cycles 1 and 4 (each cycle = 21 days); and at any time during study treatment/early discontinuation visit (approximately 40 months)

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	116		
Units: Percentage of Participants				
number (not applicable)	0	2.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization to clinical cutoff date of 15 months

Adverse event reporting additional description:

The safety population is defined as all patients who received at least one dose of the study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Trastuzumab Emtansine + Atezolizumab

Reporting group description:

Atezolizumab 1200 milligrams (mg) intravenous (IV) infusion followed by trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the Sponsor (approximately 40 months)

Reporting group title	Trastuzumab Emtansine + Placebo

Reporting group description:

Placebo matched to atezolizumab followed by trastuzumab emtansine 3.6 mg/kg IV infusion on Day 1 Cycle 1 and thereafter on Day 1 of each 21-day cycle until disease progression, unmanageable toxicity, or study termination by the sponsor (approximately 40 months)

Serious adverse events	Trastuzumab Emtansine + Atezolizumab	Trastuzumab Emtansine + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 132 (32.58%)	13 / 68 (19.12%)	
number of deaths (all causes)	13	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	10 / 132 (7.58%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	9 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza Like Illness			
subjects affected / exposed	2 / 132 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 132 (1.52%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			

subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic Attack			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 132 (2.27%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	3 / 132 (2.27%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lower Limb Fracture			

subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haemorrhage			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 132 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Oedema			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Peripheral			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 132 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated Intravascular Coagulation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Histioytosis Haematophagic			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 132 (2.27%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	0 / 132 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 132 (0.76%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intra-Abdominal Haemorrhage			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Mass			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of Jaw			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in Extremity			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	3 / 132 (2.27%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 132 (2.27%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Jaw			

subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cellulitis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Infection			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious Pleural Effusion			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			

subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 132 (0.76%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 132 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab Emtansine + Atezolizumab	Trastuzumab Emtansine + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 132 (96.21%)	62 / 68 (91.18%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 132 (2.27%)	4 / 68 (5.88%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	23 / 132 (17.42%)	4 / 68 (5.88%)	
occurrences (all)	27	4	
Chills			
subjects affected / exposed	19 / 132 (14.39%)	6 / 68 (8.82%)	
occurrences (all)	24	8	
Fatigue			
subjects affected / exposed	49 / 132 (37.12%)	29 / 68 (42.65%)	
occurrences (all)	70	41	
Influenza Like Illness			

subjects affected / exposed	11 / 132 (8.33%)	8 / 68 (11.76%)	
occurrences (all)	13	8	
Mucosal Inflammation			
subjects affected / exposed	12 / 132 (9.09%)	1 / 68 (1.47%)	
occurrences (all)	16	1	
Oedema Peripheral			
subjects affected / exposed	7 / 132 (5.30%)	3 / 68 (4.41%)	
occurrences (all)	8	3	
Pyrexia			
subjects affected / exposed	40 / 132 (30.30%)	11 / 68 (16.18%)	
occurrences (all)	59	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 132 (14.39%)	10 / 68 (14.71%)	
occurrences (all)	21	11	
Dyspnoea			
subjects affected / exposed	13 / 132 (9.85%)	7 / 68 (10.29%)	
occurrences (all)	16	8	
Epistaxis			
subjects affected / exposed	22 / 132 (16.67%)	10 / 68 (14.71%)	
occurrences (all)	25	12	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 132 (1.52%)	4 / 68 (5.88%)	
occurrences (all)	2	4	
Insomnia			
subjects affected / exposed	9 / 132 (6.82%)	2 / 68 (2.94%)	
occurrences (all)	9	2	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	20 / 132 (15.15%)	11 / 68 (16.18%)	
occurrences (all)	24	13	
Aspartate Aminotransferase Increased			
subjects affected / exposed	27 / 132 (20.45%)	11 / 68 (16.18%)	
occurrences (all)	32	14	
Blood Alkaline Phosphatase			

Increased			
subjects affected / exposed	6 / 132 (4.55%)	6 / 68 (8.82%)	
occurrences (all)	7	7	
Weight Decreased			
subjects affected / exposed	10 / 132 (7.58%)	3 / 68 (4.41%)	
occurrences (all)	10	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 132 (5.30%)	2 / 68 (2.94%)	
occurrences (all)	8	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 132 (6.82%)	8 / 68 (11.76%)	
occurrences (all)	14	9	
Dysgeusia			
subjects affected / exposed	7 / 132 (5.30%)	5 / 68 (7.35%)	
occurrences (all)	8	6	
Headache			
subjects affected / exposed	35 / 132 (26.52%)	17 / 68 (25.00%)	
occurrences (all)	49	27	
Neuropathy Peripheral			
subjects affected / exposed	18 / 132 (13.64%)	6 / 68 (8.82%)	
occurrences (all)	20	7	
Paraesthesia			
subjects affected / exposed	7 / 132 (5.30%)	2 / 68 (2.94%)	
occurrences (all)	14	2	
Peripheral Sensory Neuropathy			
subjects affected / exposed	10 / 132 (7.58%)	3 / 68 (4.41%)	
occurrences (all)	10	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 132 (12.12%)	2 / 68 (2.94%)	
occurrences (all)	18	3	
Neutropenia			
subjects affected / exposed	9 / 132 (6.82%)	4 / 68 (5.88%)	
occurrences (all)	16	4	

Thrombocytopenia			
subjects affected / exposed	35 / 132 (26.52%)	9 / 68 (13.24%)	
occurrences (all)	75	16	
Eye disorders			
Dry Eye			
subjects affected / exposed	8 / 132 (6.06%)	4 / 68 (5.88%)	
occurrences (all)	8	4	
Lacrimation Increased			
subjects affected / exposed	7 / 132 (5.30%)	1 / 68 (1.47%)	
occurrences (all)	7	1	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	14 / 132 (10.61%)	3 / 68 (4.41%)	
occurrences (all)	16	3	
Constipation			
subjects affected / exposed	25 / 132 (18.94%)	10 / 68 (14.71%)	
occurrences (all)	32	14	
Diarrhoea			
subjects affected / exposed	31 / 132 (23.48%)	12 / 68 (17.65%)	
occurrences (all)	43	13	
Dyspepsia			
subjects affected / exposed	12 / 132 (9.09%)	3 / 68 (4.41%)	
occurrences (all)	18	3	
Nausea			
subjects affected / exposed	48 / 132 (36.36%)	27 / 68 (39.71%)	
occurrences (all)	75	37	
Stomatitis			
subjects affected / exposed	9 / 132 (6.82%)	2 / 68 (2.94%)	
occurrences (all)	13	2	
Vomiting			
subjects affected / exposed	26 / 132 (19.70%)	12 / 68 (17.65%)	
occurrences (all)	35	16	
Abdominal Pain Upper			
subjects affected / exposed	9 / 132 (6.82%)	2 / 68 (2.94%)	
occurrences (all)	9	7	
Dry Mouth			

subjects affected / exposed	20 / 132 (15.15%)	8 / 68 (11.76%)	
occurrences (all)	21	9	
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	8 / 132 (6.06%)	0 / 68 (0.00%)	
occurrences (all)	9	0	
Pruritus			
subjects affected / exposed	18 / 132 (13.64%)	5 / 68 (7.35%)	
occurrences (all)	22	6	
Rash			
subjects affected / exposed	27 / 132 (20.45%)	7 / 68 (10.29%)	
occurrences (all)	34	11	
Endocrine disorders			
Hypothryroidism			
subjects affected / exposed	12 / 132 (9.09%)	2 / 68 (2.94%)	
occurrences (all)	13	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 132 (12.88%)	6 / 68 (8.82%)	
occurrences (all)	18	7	
Back Pain			
subjects affected / exposed	13 / 132 (9.85%)	6 / 68 (8.82%)	
occurrences (all)	14	7	
Muscle Spasms			
subjects affected / exposed	5 / 132 (3.79%)	6 / 68 (8.82%)	
occurrences (all)	5	7	
Musculoskeletal Pain			
subjects affected / exposed	9 / 132 (6.82%)	2 / 68 (2.94%)	
occurrences (all)	10	2	
Myalgia			
subjects affected / exposed	22 / 132 (16.67%)	9 / 68 (13.24%)	
occurrences (all)	24	15	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 132 (6.82%)	1 / 68 (1.47%)	
occurrences (all)	10	3	

Upper Resipiratory Tract Infection			
subjects affected / exposed	15 / 132 (11.36%)	5 / 68 (7.35%)	
occurrences (all)	18	5	
Urinary Tract Infection			
subjects affected / exposed	6 / 132 (4.55%)	6 / 68 (8.82%)	
occurrences (all)	6	9	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	28 / 132 (21.21%)	11 / 68 (16.18%)	
occurrences (all)	43	13	
Hypokalemia			
subjects affected / exposed	9 / 132 (6.82%)	4 / 68 (5.88%)	
occurrences (all)	11	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2016	Study schema related to study drug discontinuation has been clarified with regards to discontinuation for toxicity and treatment beyond progression. Safety, pharmacokinetic, and immunogenicity endpoints for the study have been clarified. Bone scan requirements have been clarified with regards to frequency. On the basis of updated clinical data regarding the atezolizumab half-life of 27 days, the abstinence period and when to use of live vaccine was revised. Tumor specimen requirements have been clarified. Inclusion criteria related to local laboratory assessments for screening have been clarified. Exclusion criteria related to cardiopulmonary dysfunction, patients with severe infection, leptomeningeal disease, washout period of prior anti-cancer therapy has been added/revised. The unblinding of treatment assignment at the patient level for non-safety reasons has been clarified with regards to when this is permitted. The recalculation of the trastuzumab emtansine dose at every cycle based on a patient's weight has been clarified. The frequency and type of tumor assessments to be performed after the screening period have been specified. On the basis of a review of clinical data, Epstein Barr virus testing is no longer required and has been removed from the protocol. The alpha spending function to be used for testing the primary efficacy endpoint PFS to account for the conduct of one interim analysis was changed from a gamma function with parameter -8 to a gamma function with parameter -1.
09 August 2017	The interim analysis for PFS has been removed. The number of PFS events for the primary PFS analysis has been increased from 95 to 115. The first analysis of OS will be performed at the time of the primary PFS analysis. Another update for OS will be performed at approximately 12 months after the primary PFS analysis. The final OS analysis will be performed at approximately 24 months after the primary PFS analysis or when ~50% OS events from 200 patients can be obtained, whichever occurs first. The Sponsor may consider additional OS updates beyond 24 months after primary PFS analysis if more mature OS data are requested by the Health Authority. The changes allow for a better understanding of the therapeutic effects of the experimental treatment on OS and provide more mature data for benefit-risk assessment with the additional follow-up period for survival data. The assumed median PFS time for the control arm, trastuzumab emtansine plus placebo, has been changed from 9.6 months (observed in EMILIA study) to 6.2 months (observed in TH3RESA study) to reflect the observed prior treatment demographics of patients enrolled in the study. The estimated time for primary PFS analysis has been changed from approximately 19−21 months after first patient enrolled to approximately 15−17 months after first patient enrolled, due to the updated assumption of median PFS time for the control arm and the updated number of events for primary PFS analysis. The pregnancy reporting process has been clarified and the safety risks for trastuzumab emtansine and atezolizumab have been updated. Brain assessment, brain computed tomography/magnetic resonance imagining requirements, and event reporting for hospitalization have been clarified and the reporting of the term "sudden death" has been updated to also require the presumed cause of death. The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported