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	06 February 2020

Results information

Result version number	v2 (current)
This version publication date	14 February 2021
First version publication date	26 December 2018
Version creation reason	

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	06 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2020
Was the trial ended prematurely?	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	58

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	Investigator, Subject

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	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.

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.

Number of subjects in period 1	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab
Started	69	133
Completed	0	0
Not completed	69	133
Consent withdrawn by subject	16	22
Death	20	39
Progressive Disease	-	1
Study Terminated by Sponsor	32	69
Symptomatic deterioration/clinical progression	1	-
Lost to follow-up	-	1
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			
Asian	23	49	72
Black or African American	1	5	6
Native Hawaiian or other Pacific Islander	0	1	1
White	44	72	116
Multiple	0	1	1
Unknown	1	5	6
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	10	11

Not Hispanic or Latino	66	114	180
Not Stated	1	4	5
Unknown	1	5	6

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 study completion, approximately 40 months

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: This is the primary safety endpoint. Typically statistical testing is only applied to efficacy endpoints, and for safety endpoints only summary statistics will be provided.

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)	97.0	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 = Median and corresponding 95% CI could not be estimated as too few participants had an event.

End point type	Secondary

End point timeframe:

Baseline up to study completion or death, whichever occurs first, approximately 40 months

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 (9999 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	= 0.2934
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.3

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 approximately 15 months

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	132		
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 = Median and upper bound of 95% CI could not be estimated as too
few participants had an event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 15 months

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: Maximum Serum Concentration (Cmax) of Trastuzumab Emtansine

End point title	Maximum Serum Concentration (Cmax) of Trastuzumab Emtansine

End point description:

Average post infusion Trastuzumab Emtansine concentration.

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)

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	110		
Units: ug/mL				
geometric mean (geometric coefficient of variation)	73.2 (± 47.5)	63.9 (± 116.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Deacetyl Mercapto 1-Oxopropyl Maytansine (DM1)

End point title	Cmax of Deacetyl Mercapto 1-Oxopropyl Maytansine (DM1)

End point description:

Average post infusion Deacetyl Mercapto 1-Oxopropyl Maytansine concentration of trastuzumab emtansine infusion

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)

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	37		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	3.19 (± 84.7)	4.21 (± 89.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Total Trastuzumab

End point title	Cmax of Total Trastuzumab

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)

End point values	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	110		
Units: ug/mL				
geometric mean (geometric coefficient of variation)	86.5 (± 26.4)	79.5 (± 58.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Atezolizumab

End point title	Cmax of Atezolizumab[2]

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:

[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: Atezolizumab was being analyzed and thus is only applicable to the arm in which it was administered.

End point values	Trastuzumab Emtansine + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: ug/mL				
geometric mean (geometric coefficient of variation)	626 (± 23.0)			

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[3]

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:

[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: Atezolizumab was being analyzed and thus is only applicable to the arm in which it was administered.

End point values	Trastuzumab Emtansine + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	131			
Units: Percentage of participants				
number (not applicable)	18.3			

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	60	129		
Units: Percentage of Participants				
number (not applicable)	0	2.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to study completion, approximately 40 months

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

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 (up to study duration of 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 (up to study duration of approximately 40 months)

Serious adverse events	Trastuzumab Emtansine + Atezolizumab	Trastuzumab Emtansine + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 133 (39.10%)	16 / 67 (23.88%)	
number of deaths (all causes)	42	22	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic adenoma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (7.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	9 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
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 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	2 / 133 (1.50%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 133 (1.50%)	1 / 67 (1.49%)	
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 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 133 (2.26%)	0 / 67 (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 / 133 (2.26%)	0 / 67 (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			
Hip fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Seizure			

subjects affected / exposed	1 / 133 (0.75%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	2 / 133 (1.50%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 133 (0.75%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
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 / 133 (1.50%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
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 / 133 (2.26%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 133 (0.75%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 133 (0.00%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

IgA nephropathy			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (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 / 133 (0.00%)	1 / 67 (1.49%)	
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 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 133 (3.01%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 133 (1.50%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Breast cellulitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (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 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 133 (0.75%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	3 / 133 (2.26%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 133 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 133 (0.75%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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	130 / 133 (97.74%)	62 / 67 (92.54%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 133 (3.01%)	4 / 67 (5.97%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	23 / 133 (17.29%)	5 / 67 (7.46%)	
occurrences (all)	35	6	
Chills			
subjects affected / exposed	19 / 133 (14.29%)	6 / 67 (8.96%)	
occurrences (all)	27	8	
Fatigue			
subjects affected / exposed	53 / 133 (39.85%)	30 / 67 (44.78%)	
occurrences (all)	87	43	
Pyrexia			

subjects affected / exposed	44 / 133 (33.08%)	12 / 67 (17.91%)	
occurrences (all)	72	18	
Influenza like illness			
subjects affected / exposed	12 / 133 (9.02%)	8 / 67 (11.94%)	
occurrences (all)	16	8	
Mucosal inflammation			
subjects affected / exposed	16 / 133 (12.03%)	1 / 67 (1.49%)	
occurrences (all)	21	1	
Oedema peripheral			
subjects affected / exposed	7 / 133 (5.26%)	4 / 67 (5.97%)	
occurrences (all)	9	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 133 (18.80%)	10 / 67 (14.93%)	
occurrences (all)	28	12	
Dyspnoea			
subjects affected / exposed	16 / 133 (12.03%)	5 / 67 (7.46%)	
occurrences (all)	19	6	
Epistaxis			
subjects affected / exposed	28 / 133 (21.05%)	10 / 67 (14.93%)	
occurrences (all)	39	13	
Oropharyngeal pain			
subjects affected / exposed	7 / 133 (5.26%)	1 / 67 (1.49%)	
occurrences (all)	8	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 133 (1.50%)	6 / 67 (8.96%)	
occurrences (all)	2	6	
Insomnia			
subjects affected / exposed	14 / 133 (10.53%)	2 / 67 (2.99%)	
occurrences (all)	15	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	31 / 133 (23.31%)	13 / 67 (19.40%)	
occurrences (all)	44	18	
Aspartate aminotransferase increased			

subjects affected / exposed	40 / 133 (30.08%)	14 / 67 (20.90%)	
occurrences (all)	56	19	
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 133 (8.27%)	6 / 67 (8.96%)	
occurrences (all)	12	8	
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 133 (5.26%)	2 / 67 (2.99%)	
occurrences (all)	7	2	
Weight decreased			
subjects affected / exposed	13 / 133 (9.77%)	3 / 67 (4.48%)	
occurrences (all)	13	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	10 / 133 (7.52%)	3 / 67 (4.48%)	
occurrences (all)	14	9	
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 133 (13.53%)	9 / 67 (13.43%)	
occurrences (all)	18	10	
Dysgeusia			
subjects affected / exposed	6 / 133 (4.51%)	5 / 67 (7.46%)	
occurrences (all)	6	6	
Headache			
subjects affected / exposed	38 / 133 (28.57%)	17 / 67 (25.37%)	
occurrences (all)	62	27	
Paraesthesia			
subjects affected / exposed	9 / 133 (6.77%)	2 / 67 (2.99%)	
occurrences (all)	16	2	
Neuropathy peripheral			
subjects affected / exposed	18 / 133 (13.53%)	7 / 67 (10.45%)	
occurrences (all)	20	8	
Peripheral sensory neuropathy			
subjects affected / exposed	11 / 133 (8.27%)	5 / 67 (7.46%)	
occurrences (all)	11	6	
Polyneuropathy			

subjects affected / exposed	2 / 133 (1.50%)	4 / 67 (5.97%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 133 (18.05%)	6 / 67 (8.96%)	
occurrences (all)	30	7	
Neutropenia			
subjects affected / exposed	13 / 133 (9.77%)	4 / 67 (5.97%)	
occurrences (all)	21	4	
Thrombocytopenia			
subjects affected / exposed	42 / 133 (31.58%)	12 / 67 (17.91%)	
occurrences (all)	105	22	
Eye disorders			
Dry eye			
subjects affected / exposed	11 / 133 (8.27%)	4 / 67 (5.97%)	
occurrences (all)	12	4	
Lacrimation increased			
subjects affected / exposed	7 / 133 (5.26%)	1 / 67 (1.49%)	
occurrences (all)	9	1	
Vision blurred			
subjects affected / exposed	7 / 133 (5.26%)	1 / 67 (1.49%)	
occurrences (all)	8	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	29 / 133 (21.80%)	10 / 67 (14.93%)	
occurrences (all)	38	15	
Diarrhoea			
subjects affected / exposed	34 / 133 (25.56%)	15 / 67 (22.39%)	
occurrences (all)	50	18	
Dyspepsia			
subjects affected / exposed	14 / 133 (10.53%)	3 / 67 (4.48%)	
occurrences (all)	21	3	
Nausea			
subjects affected / exposed	51 / 133 (38.35%)	29 / 67 (43.28%)	
occurrences (all)	84	37	
Stomatitis			

subjects affected / exposed	13 / 133 (9.77%)	2 / 67 (2.99%)	
occurrences (all)	21	2	
Vomiting			
subjects affected / exposed	27 / 133 (20.30%)	15 / 67 (22.39%)	
occurrences (all)	36	19	
Abdominal pain			
subjects affected / exposed	17 / 133 (12.78%)	3 / 67 (4.48%)	
occurrences (all)	20	3	
Abdominal pain upper			
subjects affected / exposed	10 / 133 (7.52%)	3 / 67 (4.48%)	
occurrences (all)	10	8	
Dry mouth			
subjects affected / exposed	22 / 133 (16.54%)	9 / 67 (13.43%)	
occurrences (all)	23	10	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	23 / 133 (17.29%)	4 / 67 (5.97%)	
occurrences (all)	30	5	
Rash			
subjects affected / exposed	32 / 133 (24.06%)	6 / 67 (8.96%)	
occurrences (all)	42	11	
Dry skin			
subjects affected / exposed	11 / 133 (8.27%)	0 / 67 (0.00%)	
occurrences (all)	12	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	18 / 133 (13.53%)	3 / 67 (4.48%)	
occurrences (all)	19	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 133 (19.55%)	8 / 67 (11.94%)	
occurrences (all)	37	9	
Myalgia			
subjects affected / exposed	24 / 133 (18.05%)	10 / 67 (14.93%)	
occurrences (all)	26	16	
Back pain			

subjects affected / exposed	15 / 133 (11.28%)	8 / 67 (11.94%)	
occurrences (all)	19	9	
Bone pain			
subjects affected / exposed	8 / 133 (6.02%)	3 / 67 (4.48%)	
occurrences (all)	8	8	
Muscle spasms			
subjects affected / exposed	10 / 133 (7.52%)	7 / 67 (10.45%)	
occurrences (all)	13	8	
Musculoskeletal pain			
subjects affected / exposed	10 / 133 (7.52%)	6 / 67 (8.96%)	
occurrences (all)	12	6	
Pain in extremity			
subjects affected / exposed	9 / 133 (6.77%)	4 / 67 (5.97%)	
occurrences (all)	10	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 133 (11.28%)	6 / 67 (8.96%)	
occurrences (all)	20	8	
Sinusitis			
subjects affected / exposed	7 / 133 (5.26%)	2 / 67 (2.99%)	
occurrences (all)	9	2	
Upper respiratory tract infection			
subjects affected / exposed	18 / 133 (13.53%)	9 / 67 (13.43%)	
occurrences (all)	28	12	
Urinary tract infection			
subjects affected / exposed	9 / 133 (6.77%)	8 / 67 (11.94%)	
occurrences (all)	10	10	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 133 (22.56%)	12 / 67 (17.91%)	
occurrences (all)	52	14	
Hypokalaemia			
subjects affected / exposed	13 / 133 (9.77%)	4 / 67 (5.97%)	
occurrences (all)	16	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.

28 February 2018	Updated information regarding the independent data monitoring committee (iDMC) recommendation and the Sponsor's decision to unblind treatment assignment. Modifications were made to the information regarding the frequency of tumor assessments and collection of tumor assessment scans following PFS analysis. Placebo administration was removed for patients randomized to Arm A. Imaginng data used for tumor assessment would no longer be collected by the Sponsor. For participants in Arm A, the thyroid function test woul no longer be perfromed and PK and ATA samples would not be collected. Language regarding post-trial access was modified to align with current standardsd. The time period for storage of tumor tissue samples was clarified. Language was added to clarif the use of samples after withdrawl of participant consent. Language was added and modified to align with the most recent Investigator's Brochure. eCRF use of recording of death attributed to progression of metastatic breast cancer was clarified. Safety analyses and criteria related to PFS assessed using the Immune-Modified RECIST was amended to be consistent with the SAP.
30 November 2018	Blood samples would no longer be collected for the analysis of trastuzumab emtansine and atezolizumab PK and ATAs. Blood samples for biomarker analyses would no longer be collected. Text was added to clarify that the Sponsor may decide to terminate the study after the OS analysis that was planned for 12 months after the primary PFS analysis and the duration of the study ws clarified to be a maximum of 40 months. The option to conduct OS analysis beyond 24 months after the primary analysis was removed. Inclusion criteria was modified to specify when women must refrain from donating eggs. Instructions regardng participant withdrawl from the Roche Bosample Repositiory after site closure was modified to indicate that the investigator must inform the Sponsor of participant withdrawl. The lists of risks for atezolizumab and guidelines for managing participants who experienced atezolizumab AEs were revised to include nephritis. Language was added for consistency with Roche's current data retention policy.
25 October 2019	Background information regarding atezolizumab was updated. The list of atezolizumab risks was updated as well as the guidelines for managing participants who experience-atezolizumab AEs to include myositis. "Immune-related" was changed to "Immune-mediated" when describing events associated with atezolizumab. To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), language regarding atezolizumab risks was revised to remove the description and management guidelines for systemic immune activation and to add descriptions and management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome. The medical monitor changed. Language was updated to indicate that therapeutic or elective abortions were not considered AEs and that the underlying toxicity should be reported as a seriours AE. Language was added to clarify that all abortions needed to be reported on the Clinical Trial Pregnancy Reporting Form paper. Language was added for consistency with Roche's current data retention policy, and to indicate that the study would comply wih applicable local, regional. and national laws. Language was revised to clarify that the datd from this study would not be limited to 2 clinical trail registries and that redacted Clinical Study Reports and other summary reports were available upon request. To address a request by the French ANSM, the atezolizumab AE management guidelines were revised to add laboratory and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported