Clinical trial results:
A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase III Study of the Efficacy and Safety of Trastuzumab Emtansine in Combination with Atezolizumab or Placebo in Patients with HER2-Positive and PD-L1-Positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab- (+/- Pertuzumab) and Taxane-Based Therapy

Summary

EudraCT number	2020-002818-41
Trial protocol	SI DE PT NO HU FI PL FR IT
Global end of trial date	19 June 2024

Results information

Result version number	v1 (current)
This version publication date	28 June 2025
First version publication date	28 June 2025

Trial information

Trial identification

Sponsor protocol code	MO42319

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04740918
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
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	Final
Date of interim/final analysis	19 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo in participants with human epidermal growth factor receptor 2 (HER2)-positive and programmed death-ligand 1 (PD-L1) -positive locally advanced (LABC) or metastatic breast cancer (MBC).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	China: 31
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Philippines: 5
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Türkiye: 17
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Croatia: 2

Worldwide total number of subjects	96
EEA total number of subjects	21

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)	84
From 65 to 84 years	11
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 96 participants with HER2-positive and PD-L1-positive LABC or MBC took part in the study across 52 investigative sites in 19 countries from 07 June 2021 to 19 June 2024.

Pre-assignment

Screening details:

Participants were randomized in 1:1 ratio to receive trastuzumab emtansine + placebo (Arm 1) or trastuzumab emtansine + atezolizumab (Arm 2).

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, Monitor, Carer, Data analyst, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab Emtansine 3.6 mg + Placebo

Arm description:

Participants received trastuzumab emtansine, 3.6 milligrams (mg), every 3 weeks (Q3W) as an intravenous (IV) infusion in combination with atezolizumab matching placebo, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

Arm type	Experimental
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:

Atezolizumab matching placebo dose, Q3W as IV infusion.

Investigational medicinal product name	Trastuzumab Emtansine
Investigational medicinal product code	RO5304020
Other name	Kadcyla
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab Emtansine, 3.6 mg, Q3W as IV infusion.

Arm title	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg

Arm description:

Participants received trastuzumab emtansine, 3.6 mg, Q3W as an IV infusion in combination with atezolizumab, 1200 mg, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	RO5541267
Other name	Tecentriq, MPDL3280A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: Atezolizumab, 1200 mg, Q3W as IV infusion.	
Investigational medicinal product name	Trastuzumab Emtansine
Investigational medicinal product code	RO5304020
Other name	Kadcyla
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Trastuzumab Emtansine, 3.6 mg, Q3W as IV infusion.	

Number of subjects in period 1	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Started	50	46
Completed	0	0
Not completed	50	46
Consent withdrawn by subject	5	4
Death	3	6
Study Terminated by Sponsor	41	32
Lost to follow-up	1	3
Progressive disease	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab Emtansine 3.6 mg + Placebo
Reporting group description:	
Participants received trastuzumab emtansine, 3.6 milligrams (mg), every 3 weeks (Q3W) as an intravenous (IV) infusion in combination with atezolizumab matching placebo, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.	
Reporting group title	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Reporting group description:	
Participants received trastuzumab emtansine, 3.6 mg, Q3W as an IV infusion in combination with atezolizumab, 1200 mg, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.	

Reporting group values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg	Total
Number of subjects	50	46	96
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	53.2	50.9	
standard deviation	± 11.7	± 10.0	-
Sex: Female, Male Units: participants			
Female	50	46	96
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	4	11
Not Hispanic or Latino	42	39	81
Unknown or Not Reported	1	3	4
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	17	21	38
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	29	23	52
More than one race	1	0	1
Unknown or Not Reported	1	1	2

End points

End points reporting groups

Reporting group title	Trastuzumab Emtansine 3.6 mg + Placebo

Reporting group description:

Participants received trastuzumab emtansine, 3.6 milligrams (mg), every 3 weeks (Q3W) as an intravenous (IV) infusion in combination with atezolizumab matching placebo, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

Reporting group title	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg

Reporting group description:

Participants received trastuzumab emtansine, 3.6 mg, Q3W as an IV infusion in combination with atezolizumab, 1200 mg, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

Subject analysis set title	Trastuzumab Emtansine 3.6 mg + Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received trastuzumab emtansine, 3.6 mg, Q3W as an IV infusion in combination with atezolizumab matching placebo, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

Subject analysis set title	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received trastuzumab emtansine, 3.6 mg, Q3W as an IV infusion in combination with atezolizumab, 1200 mg, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

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

End point title	Progression-Free Survival (PFS) as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point description:

PFS was defined as the time from randomization to the first occurrence of documented disease progression (PD), as determined by the investigator according to RECIST v1.1 or death from any cause whichever occurs first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeter (mm). Median PFS was calculated using the Kaplan-Meier (KM) methodology. Data for participants without PD or death from any cause as of the data cut-off date were censored at the time of the last tumor assessment. ITT population included all participants who were randomized in the study, whether they received any study medication.

End point type	Primary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	46		

Units: months				
median (confidence interval 95%)	7.52 (6.18 to 10.94)	8.61 (5.72 to 16.92)		

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo
Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2876
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.28

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the first dose of study treatment to the time of death from any cause. Participants who are alive as of the data cut-off date of the analysis were censored at the last known date they were alive. Participants with no post-baseline information were censored at the date of randomization plus 1 day. Median OS was calculated using the KM methodology. ITT population included all participants who were randomized in the study, whether they received any study medication. 99999= median and 95% confidence interval (CI) was not estimable due to insufficient number of events. 9999=median and upper limit of 95% CI was not estimable due to insufficient number of events.

End point type	Primary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	46		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	9999 (21.29 to 9999)		

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo
Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5151
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	6.43

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR = percentage of participants with complete response (CR) or partial response (PR) on two consecutive assessments, at least 28 days apart, as determined by the investigator using RECIST v.1.1. CR = disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) having a reduction in short axis to <10 mm. PR = at least a 30% decrease in the sum of diameters (SOD) of target lesions, taking as reference the baseline SOD. Only participants with measurable disease at baseline were analyzed for this outcome measure. Participants without a post-baseline tumor assessment were considered non-responders. An estimate of the ORR and its 95% CI (Wilson score confidence interval) were calculated for each treatment arm. Subset ITT with measurable disease included all participants in the ITT with a measurable disease at baseline. ITT population included all participants who were randomized to the study, whether or not they received any study medication.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	45		
Units: percentage of participants				
number (confidence interval 95%)	49 (34.64 to	53.3 (38.04 to		

63.48)	68.07)

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo
Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.724
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.7

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was calculated for participants who had a best OR of CR/PR. DOR=time from first occurrence of documented OR until time of documented PD/death from any cause, whichever occurs first as determined by investigator assessment using RECIST. CR= disappearance of all target lesions or any pathological lymph nodes (whether target/non-target) having a reduction in short axis to <10 mm. PR=at least a 30% decrease in the SOD of target lesions, taking as reference baseline SOD. PD=at least a 20% increase in the SOD of target lesions, taking as reference smallest sum on the study including baseline (nadir). In addition to relative increase of 20%, sum must also demonstrate an absolute increase of at least 5 mm. Median DOR was calculated using KM methodology. Subset ITT with measurable disease=all participants in the ITT with a measurable disease at baseline. Number analyzed=participants with OR i.e responders. 99999=upper limit of 95%CI was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: months				

median (confidence interval 95%)	8.21 (5.72 to 99999)	15.57 (7.06 to 99999)		

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo
Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3531
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.61

Secondary: PFS in Participants With Baseline Brain Metastases as Determined by Investigator Assessment Using RECIST v1.1

End point title	PFS in Participants With Baseline Brain Metastases as Determined by Investigator Assessment Using RECIST v1.1

End point description:

PFS was defined as the time from randomization to the first occurrence of documented PD, as determined by the investigator according to RECIST v1.1 or death from any cause whichever occurs first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Median PFS was calculated using the KM methodology. ITT with brain metastasis population included all participants in ITT with brain metastasis at randomization. 99999=upper limit of 95% CI was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: months				
median (confidence interval 95%)	7.69 (4.14 to	4.78 (1.31 to		

99999)	99999)

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo
Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7175
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	6.81

Secondary: OS in Participants with Baseline Brain Metastases

End point title	OS in Participants with Baseline Brain Metastases

End point description:

OS is defined as the time from the first dose of study treatment to the time of death from any cause. Median OS was calculated using the KM methodology. ITT with brain metastasis population included all participants in ITT with brain metastasis at randomization. 99999= median and 95%CI was not estimable due to insufficient number of events. 9999= median and upper limit of 95%CI was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	9999 (9.53 to 9999)		

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo
Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3173 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	999.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	9999

Notes:

[1] - The upper limit of the 95 % CI was not estimable due to the insufficient number of events.

Secondary: Central Nervous System (CNS) PFS as Determined by Investigator Using RECIST v1.1 in Participants With Baseline CNS Metastases

End point title	Central Nervous System (CNS) PFS as Determined by Investigator Using RECIST v1.1 in Participants With Baseline CNS Metastases

End point description:

CNS PFS=time from randomization to first occurrence of documented CNS PD/first occurrence of symptomatic CNS disease as determined by investigator according to RECIST v1.1 or death from any cause whichever occurs first. PD = at least a 20% increase in SOD of target lesions, taking as reference the smallest sum in study, including baseline, in addition to relative increase of 20%, sum must also demonstrate an absolute increase of ≥5 mm. Median PFS was calculated using KM methodology. Participants who experienced non-CNS PD at time of analysis were censored at date of this progression. Participants who experienced no PD & were alive at time of analysis were censored at date of their last post-baseline tumor assessment or, if they had no post-baseline tumor assessment, on date of randomization+1 day. ITT with CNS metastasis population=all participants in ITT with CNS metastasis at randomization. 99999=upper limit of 95% CI was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: months				
median (confidence interval 95%)	10.41 (4.11 to 99999)	9.53 (1.31 to 99999)		

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo
Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8658
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	8.6

Secondary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)[2]

End point description:

An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Safety evaluable population included all participants who received at least one full or partial dose of study drug. One participant randomized to Trastuzumab Emtansine + Placebo moved to Trastuzumab Emtansine + Atezolizumab 1200 mg. Hence, has been represented in the later arm for safety analysis.

End point type	Secondary

End point timeframe:

Up to 28 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: All analysis was descriptive only and no formal hypothesis testing was done.

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49	47		
Units: percentage of participants				
number (not applicable)	93.9	97.9		

Statistical analyses

No statistical analyses for this end point

Secondary: CNS PFS as Determined by Investigator Using RECIST v1.1 in Participants Without Baseline CNS Metastases

End point title	CNS PFS as Determined by Investigator Using RECIST v1.1 in Participants Without Baseline CNS Metastases

End point description:

CNS PFS=time from randomization to first occurrence of documented CNS PD/first occurrence of symptomatic CNS disease as determined by investigator according to RECIST v1.1 or death from any cause whichever occurs first. PD=at least a 20% increase in SOD of target lesions, taking as reference the smallest sum in study, including baseline, in addition to relative increase of 20%, sum must also demonstrate an absolute increase of ≥5 mm. Participants who experienced non-CNS PD at time of analysis were censored at date of this progression. Participants who experienced no PD & were alive at time of analysis were censored at last post-baseline (PB) tumor assessment or on date of randomization+1 day (if no PB data). ITT without CNS metastases at baseline population=all participants in ITT without CNS metastasis at baseline. 9999=median & 95% CI were not estimable due to insufficient number of events. 999=median & upper limit of 95% CI were not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	999 (21.29 to 999)		

Statistical analyses

Statistical analysis title	Atezolizumab vs Placebo

Statistical analysis description:

Stratified Analysis: Local hormonal status (ER and/or PgR positive vs. ER and PgR negative/unknown)

and Disease status (visceral metastasis without brain metastasis vs. non-visceral metastasis only without brain metastasis [including locally advanced disease] vs. Brain metastasis).

Comparison groups	Trastuzumab Emtansine 3.6 mg + Placebo v Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8407
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	4.99

Other pre-specified: Mean Absolute Scores in Physical Function (PF), Role Function (RF) and Global Health Status (GHS/QoL) Scores Measured Using European Organization for Research and Treatment of Cancer (EORTC QLQ-C30)

End point title	Mean Absolute Scores in Physical Function (PF), Role Function (RF) and Global Health Status (GHS/QoL) Scores Measured Using European Organization for Research and Treatment of Cancer (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30 consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), GHS/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The PF scale has 5 questions about participant's PF and daily activities (strenuous activities, long walks, short walks, bed/chair rest & needing help with eating, dressing, washing themselves, or using the toilet). The RF scale has 2 questions about work/daily activities and hobbies/leisurely activities. The PF and RF are scored on a 4-point scale (1=Not at All to 4=Very Much). The GHS/QoL are scored on a 7-point scale (1=Very Poor to 7=Excellent). The obtained scores are linearly transformed to a score range of 0-100, where higher scores indicate a higher response level and better QoL, functioning/support.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[3] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

[4] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PFS as Determined by a Blinded Independent Central Review (BICR) Committee Using RECIST v1.1

End point title	PFS as Determined by a Blinded Independent Central Review (BICR) Committee Using RECIST v1.1

End point description:

PFS was defined as the time from randomization to the first occurrence of documented PD, as determined by the BICR committee according to RECIST v1.1 or death from any cause whichever occurs first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. As prespecified in the latest protocol, following sponsor's decision to prematurely terminate the study, analysis of PFS as determined by a BICR committee was not conducted.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[5] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

[6] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From-Baseline in PF, RF and GHS/QoL Scores Measured Using EORTC QLQ-C30

End point title	Change From-Baseline in PF, RF and GHS/QoL Scores Measured Using EORTC QLQ-C30

End point description:

EORTC QLQ-C30 consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), GHS/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).The PF scale has 5 questions about participant's PF and daily activities (strenuous activities, long walks, short walks, bed/chair rest & needing help with eating, dressing, washing themselves, or using the toilet). The RF scale has 2 questions about work/daily activities and hobbies/leisurely activities. The PF and RF are scored on a 4-point scale (1=Not at All to 4=Very Much). The GHS/QoL are scored on a 7-point scale (1=Very Poor to 7=Excellent). The obtained scores are linearly transformed to a score range of 0-100, where higher scores indicate a higher response level and better QoL, functioning/support.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

[8] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Serum Concentration (Cmax) of Trastuzumab Emtansine

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

End point description:

As prespecified in the latest protocol, following sponsor’s decision to prematurely terminate the study, pharmacokinetic (PK) objectives and outcome measures were no longer applicable. Hence sample collection was stopped, and this outcome measure was not assessed or analyzed.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: nanograms/milliliters (ng/mL)				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

[10] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants with Clinically Meaningful Deterioration in PF, RF and GHS/QoL Measured Using EORTC QLQ-C30

End point title	Percentage of Participants with Clinically Meaningful Deterioration in PF, RF and GHS/QoL Measured Using EORTC QLQ-C30

End point description:

EORTC QLQ-C30 consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), GHS/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).The PF scale has 5 questions about participant's PF and daily activities (strenuous activities, long walks, short walks, bed/chair rest & needing help with eating, dressing, washing themselves, or using the toilet). The RF scale has 2 questions about work/daily activities and hobbies/leisurely activities. The PF and RF are scored on a 4-point scale (1=Not at All to 4=Very Much). The GHS/QoL are scored on a 7-point scale (1=Very Poor to 7=Excellent). The obtained scores are linearly transformed to a score range of 0-100, where higher scores indicate a higher response level and better QoL, functioning/support.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: percentage of participants				

Notes:

[11] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

[12] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cmax of Atezolizumab

End point title	Cmax of Atezolizumab

End point description:

As prespecified in the latest protocol, following sponsor's decision to prematurely terminate the study, PK objectives and outcome measures were no longer applicable. Hence sample collection was stopped, and this outcome measure was not assessed or analyzed.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[13] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.
[14] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants With Anti-Drug Antibodies (ADAs) to Trastuzumab Emtansine

End point title	Percentage of Participants With Anti-Drug Antibodies (ADAs) to Trastuzumab Emtansine

End point description:

As prespecified in the latest protocol, following sponsor's decision to prematurely terminate the study, immunogenicity objectives and outcome measures were no longer applicable. Hence sample collection was stopped, and this outcome measure was not assessed or analyzed.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: percentage of participants				

Notes:

[15] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.
[16] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants With ADAs to Atezolizumab

End point title	Percentage of Participants With ADAs to Atezolizumab

End point description:

As prespecified in the latest protocol, following sponsor's decision to prematurely terminate the study, immunogenicity objectives and outcome measures were no longer applicable. Hence sample collection was stopped, and this outcome measure was not assessed or analyzed.

End point type	Other pre-specified

End point timeframe:

Up to 28 months

End point values	Trastuzumab Emtansine 3.6 mg + Placebo	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: percentage of participants				

Notes:

[17] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

[18] - Sponsor prematurely terminated the study, and hence analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 28 months

Adverse event reporting additional description:

Safety evaluable population included all participants who received at least one full or partial dose of study drug. One participant randomized to Trastuzumab Emtansine + Placebo moved to Trastuzumab Emtansine + Atezolizumab 1200 mg. Hence, has been represented in the later arm for safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg

Reporting group description:

Participants received trastuzumab emtansine, 3.6 mg, Q3W as an IV infusion in combination with atezolizumab, 1200 mg, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

Reporting group title	Trastuzumab Emtansine 3.6 mg + Placebo

Reporting group description:

Participants received trastuzumab emtansine, 3.6 mg, Q3W as an IV infusion in combination with atezolizumab matching placebo, Q3W as an IV infusion on Day 1 of each 21-day cycle until radiographic disease progression, intolerable toxicity, withdrawal of consent, death or study termination by the sponsor.

Serious adverse events	Trastuzumab Emtansine 3.6 mg + Atezolizumab 1200 mg	Trastuzumab Emtansine 3.6 mg + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 47 (29.79%)	9 / 49 (18.37%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events	0	0	
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 47 (4.26%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Humerus fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 47 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (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	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal inflammation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (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 function abnormal			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Vascular device infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	1 / 47 (2.13%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 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 3.6 mg + Atezolizumab 1200 mg	Trastuzumab Emtansine 3.6 mg + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 47 (97.87%)	46 / 49 (93.88%)	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	3 / 47 (6.38%)	2 / 49 (4.08%)	
occurrences (all)	3	2	
Asthenia			
subjects affected / exposed	7 / 47 (14.89%)	4 / 49 (8.16%)	
occurrences (all)	9	7	
Pyrexia			
subjects affected / exposed	11 / 47 (23.40%)	3 / 49 (6.12%)	
occurrences (all)	16	4	
Fatigue			
subjects affected / exposed	11 / 47 (23.40%)	11 / 49 (22.45%)	
occurrences (all)	16	15	
Influenza like illness			
subjects affected / exposed	1 / 47 (2.13%)	3 / 49 (6.12%)	
occurrences (all)	1	4	
Oedema peripheral			
subjects affected / exposed	3 / 47 (6.38%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	7 / 47 (14.89%)	7 / 49 (14.29%)	
occurrences (all)	8	10	
Cough			

subjects affected / exposed	5 / 47 (10.64%)	7 / 49 (14.29%)	
occurrences (all)	6	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 47 (6.38%)	2 / 49 (4.08%)	
occurrences (all)	3	2	
Insomnia			
subjects affected / exposed	4 / 47 (8.51%)	5 / 49 (10.20%)	
occurrences (all)	4	6	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	10 / 47 (21.28%)	2 / 49 (4.08%)	
occurrences (all)	28	2	
Weight decreased			
subjects affected / exposed	5 / 47 (10.64%)	3 / 49 (6.12%)	
occurrences (all)	6	3	
Lymphocyte count decreased			
subjects affected / exposed	5 / 47 (10.64%)	2 / 49 (4.08%)	
occurrences (all)	16	2	
Lipase increased			
subjects affected / exposed	6 / 47 (12.77%)	0 / 49 (0.00%)	
occurrences (all)	8	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	11 / 47 (23.40%)	8 / 49 (16.33%)	
occurrences (all)	19	14	
Blood bilirubin increased			
subjects affected / exposed	7 / 47 (14.89%)	2 / 49 (4.08%)	
occurrences (all)	23	5	
White blood cell count decreased			
subjects affected / exposed	7 / 47 (14.89%)	2 / 49 (4.08%)	
occurrences (all)	32	3	
Amylase increased			
subjects affected / exposed	4 / 47 (8.51%)	0 / 49 (0.00%)	
occurrences (all)	6	0	
Aspartate aminotransferase increased			

subjects affected / exposed	26 / 47 (55.32%)	23 / 49 (46.94%)	
occurrences (all)	52	33	
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 47 (23.40%)	4 / 49 (8.16%)	
occurrences (all)	19	9	
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 47 (23.40%)	6 / 49 (12.24%)	
occurrences (all)	15	8	
Blood cholesterol increased			
subjects affected / exposed	3 / 47 (6.38%)	1 / 49 (2.04%)	
occurrences (all)	5	1	
Alanine aminotransferase increased			
subjects affected / exposed	23 / 47 (48.94%)	15 / 49 (30.61%)	
occurrences (all)	52	25	
Platelet count decreased			
subjects affected / exposed	18 / 47 (38.30%)	11 / 49 (22.45%)	
occurrences (all)	40	21	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 47 (10.64%)	5 / 49 (10.20%)	
occurrences (all)	5	5	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	6 / 47 (12.77%)	1 / 49 (2.04%)	
occurrences (all)	6	1	
Headache			
subjects affected / exposed	9 / 47 (19.15%)	8 / 49 (16.33%)	
occurrences (all)	12	17	
Dizziness			
subjects affected / exposed	2 / 47 (4.26%)	3 / 49 (6.12%)	
occurrences (all)	2	5	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 47 (6.38%)	4 / 49 (8.16%)	
occurrences (all)	6	8	
Leukopenia			

subjects affected / exposed	1 / 47 (2.13%)	3 / 49 (6.12%)	
occurrences (all)	3	6	
Anaemia			
subjects affected / exposed	20 / 47 (42.55%)	10 / 49 (20.41%)	
occurrences (all)	36	19	
Thrombocytopenia			
subjects affected / exposed	12 / 47 (25.53%)	14 / 49 (28.57%)	
occurrences (all)	20	21	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 47 (34.04%)	12 / 49 (24.49%)	
occurrences (all)	30	18	
Diarrhoea			
subjects affected / exposed	4 / 47 (8.51%)	4 / 49 (8.16%)	
occurrences (all)	15	4	
Abdominal pain			
subjects affected / exposed	3 / 47 (6.38%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	8 / 47 (17.02%)	9 / 49 (18.37%)	
occurrences (all)	17	16	
Abdominal distension			
subjects affected / exposed	0 / 47 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	11 / 47 (23.40%)	4 / 49 (8.16%)	
occurrences (all)	14	6	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 47 (6.38%)	1 / 49 (2.04%)	
occurrences (all)	3	1	
Rash			
subjects affected / exposed	2 / 47 (4.26%)	3 / 49 (6.12%)	
occurrences (all)	2	4	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	7 / 47 (14.89%)	2 / 49 (4.08%)	
occurrences (all)	9	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	5 / 47 (10.64%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Arthralgia			
subjects affected / exposed	2 / 47 (4.26%)	7 / 49 (14.29%)	
occurrences (all)	2	7	
Muscle spasms			
subjects affected / exposed	4 / 47 (8.51%)	4 / 49 (8.16%)	
occurrences (all)	4	4	
Myalgia			
subjects affected / exposed	5 / 47 (10.64%)	5 / 49 (10.20%)	
occurrences (all)	5	6	
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 47 (8.51%)	4 / 49 (8.16%)	
occurrences (all)	5	4	
Urinary tract infection			
subjects affected / exposed	3 / 47 (6.38%)	3 / 49 (6.12%)	
occurrences (all)	4	6	
Upper respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	7 / 49 (14.29%)	
occurrences (all)	1	7	
Influenza			
subjects affected / exposed	1 / 47 (2.13%)	3 / 49 (6.12%)	
occurrences (all)	1	3	
Sinusitis			
subjects affected / exposed	1 / 47 (2.13%)	3 / 49 (6.12%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 49 (0.00%)	
occurrences (all)	3	0	

Hyponatraemia			
subjects affected / exposed	6 / 47 (12.77%)	1 / 49 (2.04%)	
occurrences (all)	15	1	
Hyperglycaemia			
subjects affected / exposed	5 / 47 (10.64%)	0 / 49 (0.00%)	
occurrences (all)	5	0	
Hypokalaemia			
subjects affected / exposed	14 / 47 (29.79%)	2 / 49 (4.08%)	
occurrences (all)	40	2	
Hypertriglyceridaemia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 49 (2.04%)	
occurrences (all)	5	1	
Decreased appetite			
subjects affected / exposed	5 / 47 (10.64%)	8 / 49 (16.33%)	
occurrences (all)	5	10	
Hypocalcaemia			
subjects affected / exposed	5 / 47 (10.64%)	0 / 49 (0.00%)	
occurrences (all)	9	0	
Hypophosphataemia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 49 (0.00%)	
occurrences (all)	4	0	
Hypoalbuminaemia			
subjects affected / exposed	7 / 47 (14.89%)	1 / 49 (2.04%)	
occurrences (all)	15	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2021	1. Updated to clarify that the independent Data Monitoring Committee reviewed safety data and efficacy data. 2. Inclusion and exclusion criteria were updated. 3. Updated the number of times that the NCI PRO-CTCAE patient-reported outcome questionnaire will be administered during cycles 1, 2, and 3 [from twice (Days 1 and 15) to three times (Days 1, 8, and 15)]. 4. The Schedule of Assessments has been updated to introduce additional visits for safety assessments on Day 10 (±3 days) of Cycle 1 and Cycle 2.
22 February 2022	1. Increased the window for prescreening testing from 6 months to 12 months, and revised that up to two prescreening samples can be sent for analysis 2. Updated to provide guidance for HER2 and PD-L1 assessment in participants with initially multicentric tumors (multiple tumors involving more than one quadrant) or multifocal tumors (more than one mass confined to the same quadrant as the primary tumor). 3. Clarified that the use of hormonal contraceptives and hormone releasing intrauterine devices are prohibited in women with hormone receptor-positive tumors. 4. Updated to add a time window (+/- 10 minutes) for the infusions of trastuzumab emtansine, and guidance on the premedications that can be used for the second and subsequent infusions of trastuzumab emtansine have been added
02 March 2023	1. Revisions have been made to the study objectives to indicate which objectives are no longer applicable and the corresponding analyses that were no longer be performed. 2. The end of study and length of study have been updated. 3. The planned analyses for both PFS and OS in the context of the premature study termination have been clarified, as well as the impact of the premature study termination on the study sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 June 2024	The Sponsor decided to prematurely terminate the study due to a lower-than-expected enrollment rate.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The Sponsor decided to prematurely terminate the study due to a lower-than-expected enrollment rate.

Notes: