Clinical trial results:
A Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a, an anti-HER2-antibody drug conjugate, versus ado-trastuzumab emtansine (T-DM1) for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane

Summary

EudraCT number	2018-000222-61
Trial protocol	GB BE FR ES DE IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	09 June 2022
First version publication date	09 June 2022

Trial information

Trial identification

Sponsor protocol code	DS8201-A-U302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03529110
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo Inc.
Sponsor organisation address	211 Mt. Airy Rd., Basking Ridge, United States, 07920
Public contact	Global Clinical Director, Daiichi Sankyo Inc., 908 992-6400, CTRinfo@dsi.com
Scientific contact	Global Clinical Director, Daiichi Sankyo Inc., 908 992-6400, CTRinfo@dsi.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	21 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2021
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of DS 8201a to T-DM1 as measured by progression-free survival (PFS).

Protection of trial subjects:

The study protocol, amendments, the informed consent form(s) (ICF[s]), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). The study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Brazil: 63
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	China: 65
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Hong Kong: 21
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Japan: 68
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 84
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Taiwan: 71
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	524
EEA total number of subjects	93

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)	418
From 65 to 84 years	106
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 524 participants were enrolled & treated at study sites in 14 countries. Primary results reported is from first participant randomized up to data cutoff date of 21 May 2021. The results presented are based on primary analysis up to 33 months. Data collection is still on-going & additional results will be provided after study completion.

Pre-assignment

Screening details:

A total of 699 participants were screened and 524 participants enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab Deruxtecan (T-DXd)

Arm description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W).

Arm type	Experimental
Investigational medicinal product name	trastuzumab deruxtecan
Investigational medicinal product code	
Other name	T-DXd, DS-8201a, Enhertu®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

T-DXd is sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered intravenously.

Arm title	Ado-trastuzumab Emtansine (T-DM1)

Arm description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label.

Arm type	Experimental
Investigational medicinal product name	ado-trastuzumab emtansine
Investigational medicinal product code	
Other name	T-DM1, KADCYLA®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The treatment will be in accordance with the approved label.

Number of subjects in period 1	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)
Started	261	263
Completed	136	49
Not completed	125	214
Clinical progression	4	12
Physician decision	2	8
Miscellaneous	2	5
Adverse event	35	17
Progressive disease	66	158
Withdrawal by subject	13	11
Lack of efficacy	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab Deruxtecan (T-DXd)
Reporting group description:	
Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W).	
Reporting group title	Ado-trastuzumab Emtansine (T-DM1)
Reporting group description:	
Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label.	

Reporting group values	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)	Total
Number of subjects	261	263	524
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)	212	206	418
From 65-84 years	41	49	90
85 years and over	8	8	16
Age continuous Units: years			
median	54.5	54.2	
standard deviation	± 11.11	± 11.84	-
Gender categorical Units: Subjects			
Female	260	262	522
Male	1	1	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	152	162	314
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	9	19
White	71	72	143
More than one race	2	0	2
Unknown or Not Reported	26	20	46

End points

End points reporting groups

Reporting group title	Trastuzumab Deruxtecan (T-DXd)
Reporting group description:	
Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W).	
Reporting group title	Ado-trastuzumab Emtansine (T-DM1)
Reporting group description:	
Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label.	

Primary: Progression-Free Survival (PFS) Based on Blinded Independent Central Review (BICR) in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point title	Progression-Free Survival (PFS) Based on Blinded Independent Central Review (BICR) in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane[1]
End point description:	
Progression-free survival (PFS) by BICR was defined as the time from the date of enrollment to the earlier of the dates of the first objective documentation of disease progression (as per RECIST v1.1) or death due to any cause. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. Progression-free survival (PFS) was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.	
End point type	Primary
End point timeframe:	
Up to 33 months (data cut-off)	

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: No statistical analysis was performed.

End point values	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261[2]	263		
Units: months				
median (confidence interval 95%)	99.9 (18.5 to 99.9)	6.8 (5.6 to 8.2)		

Notes:

[2] - 99.9=NA, Median and upper CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point title	Overall Survival (OS) in Participants With HER2-Positive,

	Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point description:

Overall survival (OS) was defined as the time from the date of first dose of study drug to the date of death due to any cause. Overall survival (OS) was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.

End point type	Secondary

End point timeframe:

Up to 33 months (data cut-off)

End point values	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261[3]	263[4]		
Units: months				
median (confidence interval 95%)	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)		

Notes:

[3] - 99.9=NA, Median and 95% CI was not estimable due to insufficient number of events.

[4] - 99.9=NA, Median and 95% CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response Rate (ORR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point title	Percentage of Participants With Objective Response Rate (ORR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point description:

The Objective Response Rate (ORR) was defined as the percentage of participants who achieved a best overall response of confirmed Complete Response (CR) or Partial Response (PR), assessed by BICR and investigator assessment based on RECIST version 1.1. CR was defined as a disappearance of all target lesions and PR was defined as at least a 30% decrease in the sum of diameters of target lesions. Confirmed ORR is reported. Objective response rate was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.

End point type	Secondary

End point timeframe:

Up to 33 months (data cut-off)

End point values	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	263		
Units: Percentage of Participants				
number (confidence interval 95%)				
BICR	79.7 (74.3 to 84.4)	34.2 (28.5 to 40.3)		
Investigator Assessment	77.0 (71.2 to 82.0)	36.9 (31.0 to 43.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point title	Duration of Response (DoR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point description:

Duration of Response (DoR) was defined as the time from the date of the first documentation of objective response (complete response [CR] or partial response [PR]) to the date of the first objective documentation of progressive disease (PD) or death due to any cause. DoR in participants with confirmed CR/PR based on BICR and investigator assessment is reported. Duration of Response (DoR) was assessed in the Full Analysis Set of participants with confirmed CR/PR at data cut-off date of 21 May 2021.

End point type	Secondary

End point timeframe:

Up to 33 months (data cut-off)

End point values	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261[5]	263[6]		
Units: months				
median (confidence interval 95%)				
BICR	99.9 (20.3 to 99.9)	99.9 (12.6 to 99.9)		
Investigator Assessment	99.9 (20.8 to 99.9)	99.9 (14.1 to 99.9)		

Notes:

[5] - 99.9=NA, Median and upper CI was not estimable due to insufficient number of events.

[6] - 99.9=NA, Median and upper CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Based on Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point title	Progression-Free Survival (PFS) Based on Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

End point description:

Progression-free survival (PFS) by investigator assessment was defined as the time from the date of enrollment to the earlier of the dates of the first objective documentation of disease progression (as per RECIST v1.1) or death due to any cause. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. Progression-free survival (PFS) was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.

End point type	Secondary

End point timeframe:

Up to 33 months (data cut-off)

End point values	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261[7]	263		
Units: months				
median (confidence interval 95%)	25.1 (22.1 to 99.9)	7.2 (6.8 to 8.3)		

Notes:

[7] - 99.9=NA, Upper CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) were collected from the date of signing the informed consent form up to 47 days after last dose of the study drug, up 33 months.

Adverse event reporting additional description:

A Treatment-emergent adverse event (TEAE) is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after the initiating the study drug until 47 days after last dose of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Trastuzumab Deruxtecan (T-DXd)

Reporting group description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W

Reporting group title	Ado-trastuzumab Emtansine (T-DM1)

Reporting group description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label.

Serious adverse events	Trastuzumab Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 257 (19.07%)	47 / 261 (18.01%)	
number of deaths (all causes)	33	53	
number of deaths resulting from adverse events	5	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiodysplasia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Seizure			
subjects affected / exposed	2 / 257 (0.78%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 257 (1.56%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 1	
Disease progression			
subjects affected / exposed	3 / 257 (1.17%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	5 / 257 (1.95%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (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	1 / 257 (0.39%)	0 / 261 (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	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mediastinal cyst			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 257 (0.00%)	3 / 261 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy lymph gland			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain herniation			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
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	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasogenic cerebral oedema			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
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			
Anaemia			
subjects affected / exposed	2 / 257 (0.78%)	3 / 261 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 257 (0.78%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Otolithiasis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Rhegmatogenous retinal detachment			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 257 (1.95%)	2 / 261 (0.77%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 257 (0.78%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	1 / 257 (0.39%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 257 (0.39%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			

subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic atrophy			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic failure			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (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	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
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 / 257 (1.56%)	5 / 261 (1.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 257 (1.17%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 257 (0.78%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 257 (0.39%)	2 / 261 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Breast cellulitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 257 (0.78%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 257 (0.00%)	2 / 261 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	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 Deruxtecan (T-DXd)	Ado-trastuzumab Emtansine (T-DM1)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	256 / 257 (99.61%)	249 / 261 (95.40%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	75 / 257 (29.18%)	25 / 261 (9.58%)	
occurrences (all)	75	25	
Aspartate aminotransferase increased			
subjects affected / exposed	66 / 257 (25.68%)	105 / 261 (40.23%)	
occurrences (all)	66	105	
White blood cell count decreased			
subjects affected / exposed	58 / 257 (22.57%)	14 / 261 (5.36%)	
occurrences (all)	58	14	
Alanine aminotransferase increased			
subjects affected / exposed	56 / 257 (21.79%)	77 / 261 (29.50%)	
occurrences (all)	56	77	
Platelet count decreased			
subjects affected / exposed	54 / 257 (21.01%)	112 / 261 (42.91%)	
occurrences (all)	54	112	
Blood alkaline phosphatase increased			
subjects affected / exposed	35 / 257 (13.62%)	30 / 261 (11.49%)	
occurrences (all)	35	30	
Blood lactate dehydrogenase increased			
subjects affected / exposed	17 / 257 (6.61%)	35 / 261 (13.41%)	
occurrences (all)	17	35	
Blood bilirubin increased			
subjects affected / exposed	17 / 257 (6.61%)	13 / 261 (4.98%)	
occurrences (all)	17	13	
Lymphocyte count decreased			
subjects affected / exposed	14 / 257 (5.45%)	3 / 261 (1.15%)	
occurrences (all)	14	3	
Vascular disorders			

Hypertension			
subjects affected / exposed	14 / 257 (5.45%)	6 / 261 (2.30%)	
occurrences (all)	14	6	
Nervous system disorders			
Headache			
subjects affected / exposed	54 / 257 (21.01%)	38 / 261 (14.56%)	
occurrences (all)	54	38	
Dizziness			
subjects affected / exposed	32 / 257 (12.45%)	22 / 261 (8.43%)	
occurrences (all)	32	22	
Peripheral sensory neuropathy			
subjects affected / exposed	19 / 257 (7.39%)	25 / 261 (9.58%)	
occurrences (all)	19	25	
Dysgeusia			
subjects affected / exposed	15 / 257 (5.84%)	8 / 261 (3.07%)	
occurrences (all)	15	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	83 / 257 (32.30%)	43 / 261 (16.48%)	
occurrences (all)	83	43	
Neutropenia			
subjects affected / exposed	41 / 257 (15.95%)	7 / 261 (2.68%)	
occurrences (all)	41	7	
Leukopenia			
subjects affected / exposed	22 / 257 (8.56%)	8 / 261 (3.07%)	
occurrences (all)	22	8	
Lymphopenia			
subjects affected / exposed	15 / 257 (5.84%)	6 / 261 (2.30%)	
occurrences (all)	15	6	
Thrombocytopenia			
subjects affected / exposed	13 / 257 (5.06%)	31 / 261 (11.88%)	
occurrences (all)	13	31	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	74 / 257 (28.79%)	52 / 261 (19.92%)	
occurrences (all)	74	52	

Asthenia			
subjects affected / exposed	32 / 257 (12.45%)	31 / 261 (11.88%)	
occurrences (all)	32	31	
Malaise			
subjects affected / exposed	29 / 257 (11.28%)	10 / 261 (3.83%)	
occurrences (all)	29	10	
Pyrexia			
subjects affected / exposed	27 / 257 (10.51%)	39 / 261 (14.94%)	
occurrences (all)	27	39	
Oedema peripheral			
subjects affected / exposed	17 / 257 (6.61%)	9 / 261 (3.45%)	
occurrences (all)	17	9	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	195 / 257 (75.88%)	79 / 261 (30.27%)	
occurrences (all)	195	79	
Vomiting			
subjects affected / exposed	126 / 257 (49.03%)	26 / 261 (9.96%)	
occurrences (all)	126	26	
Constipation			
subjects affected / exposed	88 / 257 (34.24%)	51 / 261 (19.54%)	
occurrences (all)	88	51	
Diarrhoea			
subjects affected / exposed	75 / 257 (29.18%)	18 / 261 (6.90%)	
occurrences (all)	75	18	
Dyspepsia			
subjects affected / exposed	29 / 257 (11.28%)	16 / 261 (6.13%)	
occurrences (all)	29	16	
Abdominal pain			
subjects affected / exposed	29 / 257 (11.28%)	5 / 261 (1.92%)	
occurrences (all)	29	5	
Abdominal pain upper			
subjects affected / exposed	28 / 257 (10.89%)	12 / 261 (4.60%)	
occurrences (all)	28	12	
Gastrooesophageal reflux disease			

subjects affected / exposed	13 / 257 (5.06%)	4 / 261 (1.53%)	
occurrences (all)	13	4	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	29 / 257 (11.28%)	42 / 261 (16.09%)	
occurrences (all)	29	42	
Cough			
subjects affected / exposed	27 / 257 (10.51%)	26 / 261 (9.96%)	
occurrences (all)	27	26	
Dyspnoea			
subjects affected / exposed	21 / 257 (8.17%)	13 / 261 (4.98%)	
occurrences (all)	21	13	
Upper respiratory tract infection			
subjects affected / exposed	20 / 257 (7.78%)	15 / 261 (5.75%)	
occurrences (all)	20	15	
Oropharyngeal pain			
subjects affected / exposed	13 / 257 (5.06%)	6 / 261 (2.30%)	
occurrences (all)	13	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	95 / 257 (36.96%)	8 / 261 (3.07%)	
occurrences (all)	95	8	
Pruritus			
subjects affected / exposed	21 / 257 (8.17%)	18 / 261 (6.90%)	
occurrences (all)	21	18	
Rash			
subjects affected / exposed	16 / 257 (6.23%)	24 / 261 (9.20%)	
occurrences (all)	16	24	
Dry skin			
subjects affected / exposed	14 / 257 (5.45%)	4 / 261 (1.53%)	
occurrences (all)	14	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	18 / 257 (7.00%)	6 / 261 (2.30%)	
occurrences (all)	18	6	
Insomnia			

subjects affected / exposed	15 / 257 (5.84%)	24 / 261 (9.20%)	
occurrences (all)	15	24	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	24 / 257 (9.34%)	16 / 261 (6.13%)	
occurrences (all)	24	16	
Myalgia			
subjects affected / exposed	23 / 257 (8.95%)	16 / 261 (6.13%)	
occurrences (all)	23	16	
Arthralgia			
subjects affected / exposed	22 / 257 (8.56%)	23 / 261 (8.81%)	
occurrences (all)	22	23	
Pain in extremity			
subjects affected / exposed	21 / 257 (8.17%)	16 / 261 (6.13%)	
occurrences (all)	21	16	
Musculoskeletal pain			
subjects affected / exposed	17 / 257 (6.61%)	12 / 261 (4.60%)	
occurrences (all)	17	12	
Infections and infestations			
Stomatitis			
subjects affected / exposed	40 / 257 (15.56%)	10 / 261 (3.83%)	
occurrences (all)	40	10	
Urinary tract infection			
subjects affected / exposed	19 / 257 (7.39%)	13 / 261 (4.98%)	
occurrences (all)	19	13	
Pneumonia			
subjects affected / exposed	18 / 257 (7.00%)	9 / 261 (3.45%)	
occurrences (all)	18	9	
Pneumonitis			
subjects affected / exposed	18 / 257 (7.00%)	1 / 261 (0.38%)	
occurrences (all)	18	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	75 / 257 (29.18%)	44 / 261 (16.86%)	
occurrences (all)	75	44	
Weight decreased			

subjects affected / exposed	43 / 257 (16.73%)	16 / 261 (6.13%)	
occurrences (all)	43	16	
Hypokalaemia			
subjects affected / exposed	33 / 257 (12.84%)	26 / 261 (9.96%)	
occurrences (all)	33	26	
Hypoalbuminaemia			
subjects affected / exposed	20 / 257 (7.78%)	12 / 261 (4.60%)	
occurrences (all)	20	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2018	Clarified TEAEs section. Updated dose information & modification section and inclusion & exclusion criteria section. Updated definitions of Grade 2, 3, and 4 for specific investigations. Clarified language for timing of signed and dated written consent. Clarified details of urine pregnancy test results. Clarified details of lab procedures. Added details for PK sampling.
08 March 2019	Clarified the primary objective and updated secondary endpoints. Updated inclusion and exclusion criteria. Updated and clarified AE reporting and follow-up. Updated dose modification, screening, and lab sections. Updated PK sampling times. Updated procedures section.
26 April 2019	Clarified interstitial lung disease information.
23 April 2020	Added additional analyses of PFS and OS. Updated the secondary endpoint of OS. Updated the exploratory endpoints. Updated inclusion & exclusion criteria section. Updated general statistical considerations and dose modification sections. Updated screening and lab procedures. Clarified the PK sampling and end of treatment timing. Updated AE of Special Interest. Updated the Schedule of Events section.
25 September 2020	Updated to incorporate the COVID-19 management procedures. Updated exploratory endpoints to include PFS on next line therapy. Clarified withdrawal of consent language.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported