Clinical trial results:
A phase 3, multicenter, randomized, open-label, active-controlled trial of trastuzumab deruxtecan (T-DXd), an anti-HER2-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-Low, unresectable and/or metastatic breast cancer subjects (DESTINY-Breast04)

Summary

EudraCT number	2018-003069-33
Trial protocol	BE SE GR PT DE ES GB HU
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification

Sponsor protocol code	DS8201-A-U303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03734029
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mount Airy Rd, Basking Ridge, United States, 07920
Public contact	Contact for Clinical Trial Information, Daiichi Sankyo, Inc., +1 908-992-6400, CTRinfo@dsi.com
Scientific contact	Contact for Clinical Trial Information, Daiichi Sankyo, Inc., +1 908-992-6400, 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	11 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression-free survival (PFS) benefit of T-DXd to physician's choice in HER2-low, hormone receptor (HR)-positive breast cancer, based on blinded independent central review (BICR).

Protection of trial subjects:

The study protocol, amendments, informed consent form(s) (ICFs), and information sheets were approved by the appropriate and applicable IECs or IRBs. This 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	27 December 2018
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	Canada: 4
Country: Number of subjects enrolled	China: 62
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Japan: 85
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Korea, Republic of: 57
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	France: 56
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 30

Worldwide total number of subjects	557
EEA total number of subjects	202

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)	426
From 65 to 84 years	131
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 557 participants were enrolled and randomized to treatment at 161 study sites in the US (27 sites), Japan (18), France (16), China (15), Italy (13), Spain (12), Greece (8), Portugal (8), Republic of Korea (8), Israel (6), Switzerland (6), Austria (4), Belgium (4), Russia (3), Sweden (3), Taiwan (3), UK (3), Canada (2), and Hungary (2).

Pre-assignment

Screening details:

All participants had been previously treated with at least 1 and no more than 2 prior lines of chemotherapy in the recurrent or metastatic setting. The treatment chosen for the Physician's Choice arm was based on the label approved in the country of drug administration. The Physician's Choice group was combined to ensure an appropriate sample size.

Period 1

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

Blinding implementation details:

Randomized, open label study

Arms

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

Arm description:

Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to DS8201a with an initial dose of 5.4 mg/kg was infused for approximately 90 minutes. If there was no infusion-related reaction (IRR), doses of T-DXd after the initial dose of 5.4 mg/kg were infused for a minimum of 30 minutes.

Arm type	Experimental
Investigational medicinal product name	T-DXd
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

T-DXd 100 mg was administered intravenously (IV) at a dose of 5.4 mg/kg every 3 weeks (Q3W)

Arm title	Physician's Choice

Arm description:

Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to a physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel, and nabpaclitaxel) in which the dose, regimen, administration, and dose modification followed the label approved in the country of drug administration or the National Comprehensive Cancer Network guidelines.

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000-1250 mg/m2 PO twice daily on Days 1-14; cycled every 21 days

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

Dosage and administration details:

1.4 mg/m^2 IV on Days 1 and 8; cycled every 21 days (Refers to eribulin mesylate [1.23 mg eribulin base = 1.4 mg eribulin mesylate])

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

Dosage and administration details:

Option 1: 800-1200 mg/m^2 IV on Days 1 and 8; cycled every 21 days
Option 2: 800-1200 mg/m^2 IV on Days 1, 8, and 15; cycled every 28 days

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

Dosage and administration details:

Option 1: 175 mg/m^2 IV on Day 1; cycled every 21 days
Option 2: 80 mg/m^2 IV on Day 1 weekly

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

Dosage and administration details:

Option 1: 260 mg/m2 IV; cycled every 21 days
Option 2: 100 mg/m2 or 125 mg/m2 IV on Days 1, 8, and 15; cycled every 28 days

Number of subjects in period 1	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice
Started	373	184
Completed	58	3
Not completed	315	181
Consent withdrawn by subject	12	11
Physician decision	4	3
Randomized, but not treated	2	12
Adverse event, non-fatal	60	14
Clinical progression by investigator	10	8
Death	5	2
Not specified	2	-
Lost to follow-up	-	1
Progressive disease as per RECIST v1.1	220	130

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab Deruxtecan (T-DXd)
Reporting group description:	
Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to DS8201a with an initial dose of 5.4 mg/kg was infused for approximately 90 minutes. If there was no infusion-related reaction (IRR), doses of T-DXd after the initial dose of 5.4 mg/kg were infused for a minimum of 30 minutes.	
Reporting group title	Physician's Choice
Reporting group description:	
Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to a physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel, and nabpaclitaxel) in which the dose, regimen, administration, and dose modification followed the label approved in the country of drug administration or the National Comprehensive Cancer Network guidelines.	

Reporting group values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice	Total
Number of subjects	373	184	557
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)	290	136	426
From 65-84 years	83	48	131
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.5	56.5	
standard deviation	± 10.6	± 11.5	-
Gender categorical Units: Subjects			
Female	371	184	555
Male	2	0	2

End points

End points reporting groups

Reporting group title	Trastuzumab Deruxtecan (T-DXd)

Reporting group description:

Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to DS8201a with an initial dose of 5.4 mg/kg was infused for approximately 90 minutes. If there was no infusion-related reaction (IRR), doses of T-DXd after the initial dose of 5.4 mg/kg were infused for a minimum of 30 minutes.

Reporting group title	Physician's Choice

Reporting group description:

Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to a physician’s choice (capecitabine, eribulin, gemcitabine, paclitaxel, and nabpaclitaxel) in which the dose, regimen, administration, and dose modification followed the label approved in the country of drug administration or the National Comprehensive Cancer Network guidelines.

Primary: Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) in the Hormone Receptor- Positive Cohort in Participants With HER2-low Breast Cancer

End point title	Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) in the Hormone Receptor- Positive Cohort in Participants With HER2-low Breast Cancer

End point description:

Progression-free survival (PFS), defined as at least a 20% increase in the sum of diameters of target lesions, was assessed from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever came first. PFS was based on blinded independent central review (BICR) in the hormone receptorpositive cohort according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1. Median PFS was from Kaplan-Meier analysis. Confidence interval for median was computed using the Brookmeyer-Crowley method.

End point type	Primary

End point timeframe:

From the date of randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	163		
Units: months				
median (confidence interval 95%)				
Progression-free survival	10.1 (9.5 to 11.5)	5.4 (4.4 to 7.1)		

Statistical analyses

Statistical analysis title	Trastuzumab Deruxtecan (T-DXd), Physician's Choice
Comparison groups	Trastuzumab Deruxtecan (T-DXd) v Physician's Choice
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.5085
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4012
upper limit	0.6444

Notes:

[1] - Two-sided p-value from stratified log-rank test, Hazard ratio and 95% CI from stratified Cox proportional hazards model using stratification factors: HER2 status, number of prior lines of chemotherapy, hormone Receptor/CDK status, as defined by IXR

Secondary: Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) in Participants With HER2-low Breast Cancer (All Patients) Regardless of Hormone Receptor Status

End point title	Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) in Participants With HER2-low Breast Cancer (All Patients) Regardless of Hormone Receptor Status

End point description:

Progression-free survival (PFS), defined as at least a 20% increase in the sum of diameters of target lesions, was assessed from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever came first. PFS was based on blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1. Median PFS was from Kaplan-Meier analysis. Confidence interval for median was computed using the Brookmeyer-Crowley method.

End point type	Secondary

End point timeframe:

From the date of randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	184		
Units: months				
median (confidence interval 95%)				
Progression-free survival	9.9 (9.0 to 11.3)	5.1 (4.2 to 6.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point title	Overall Survival (OS) in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point description:

Overall survival (OS) was defined as the time from the date of randomization to the date of death due to any cause. If there was no death reported for a participant before the data cutoff for OS analysis, OS was censored at the last contact date at which the participant was known to be alive.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	163		
Units: months				
median (confidence interval 95%)				
Overall survival	23.9 (20.8 to 24.8)	17.5 (15.2 to 22.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Participants With HER2-low Breast Cancer (All Patients)

End point title	Overall Survival (OS) in Participants With HER2-low Breast Cancer (All Patients)

End point description:

Overall survival (OS) was defined as the time from the date of randomization to the date of death due to any cause. If there was no death reported for a participant before the data cutoff for OS analysis, OS was censored at the last contact date at which the participant was known to be alive.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	184		
Units: months				
median (confidence interval 95%)				
Overall survival	23.4 (20.0 to 24.8)	16.8 (14.5 to 20.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival Based on Investigator Assessment in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point title	Progression-free Survival Based on Investigator Assessment in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point description:

Progression-free survival (PFS), defined as at least a 20% increase in the sum of diameters of target lesions, was assessed from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever came first. PFS was based on investigator assessment in the hormone receptor-positive cohort according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1. Median PFS was from Kaplan-Meier analysis. Confidence interval for median was computed using the Brookmeyer-Crowley method.

End point type	Secondary

End point timeframe:

From the date of randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	163		
Units: months				
median (confidence interval 95%)				
Progression-free survival	9.6 (8.4 to 10.0)	4.2 (3.4 to 4.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival Based on Investigator Assessment in Participants With HER2-low Breast Cancer (All Patients)

End point title	Progression-free Survival Based on Investigator Assessment in Participants With HER2-low Breast Cancer (All Patients)

End point description:

Progression-free survival (PFS), defined as at least a 20% increase in the sum of diameters of target lesions, was assessed from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever came first. PFS was based on investigator assessment according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1. Median PFS was from Kaplan-Meier analysis. Confidence interval for median was computed using the Brookmeyer-

Crowley method.

End point type	Secondary

End point timeframe:

From the date of randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	184		
Units: months				
median (confidence interval 95%)				
Progression-free survival	8.8 (8.3 to 9.8)	4.2 (3.0 to 4.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response and Confirmed Objective Response Rate (ORR) in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point title	Best Overall Response and Confirmed Objective Response Rate (ORR) in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point description:

Best overall response rate and confirmed objective response rate (ORR) were assessed by blinded independent central review (BICR) and investigator assessment. Complete response (CR) was defined as a disappearance of all target lesions, partial response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions, and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD; at least a 20% increase in the sum of diameters of target lesions. Confirmed ORR is defined as the number of patients with complete and partial response and confirmed with a second assessment.

End point type	Secondary

End point timeframe:

From screening and every 6 weeks up to withdrawal of subject consent, progressive disease (PD), or unacceptable toxicity, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	163		
Units: patients				
number (not applicable)				
BICR: Complete response	12	1		
BICR: Partial response	164	26		
BICR: Stable disease	115	81		
BICR: Progressive disease	26	34		

BICR: Not evaluable	14	21		
Investigator: Complete response	5	0		
Investigator: Partial response	163	30		
Investigator: Stable disease	124	80		
Investigator: Progressive disease	28	34		
Investigator: Not evaluable	11	19		
BICR: Objective response rate	175	27		
Investigator: Objective response rate	168	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response and Confirmed Objective Response Rate (ORR) in Participants With HER2-low Breast Cancer (All Patients)

End point title	Best Overall Response and Confirmed Objective Response Rate (ORR) in Participants With HER2-low Breast Cancer (All Patients)

End point description:

Best overall response rate and confirmed objective response rate (ORR) were assessed by blinded independent central review (BICR) and investigator assessment. Complete response (CR) was defined as a disappearance of all target lesions, partial response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions, and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD; at least a 20% increase in the sum of diameters of target lesions. Confirmed ORR is defined as the number of patients with complete and partial response and confirmed with a second assessment.

End point type	Secondary

End point timeframe:

From screening and every 6 weeks up to withdrawal of subject consent, progressive disease (PD), or unacceptable toxicity, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	184		
Units: patients				
number (not applicable)				
BICR: Complete response	13	2		
BICR: Partial response	183	28		
BICR: Stable disease	129	91		
BICR: Progressive disease	31	41		
BICR: Not evaluable	17	22		
Investigator: Complete response	6	0		
Investigator: Partial response	187	31		
Investigator: Stable disease	135	93		
Investigator: Progressive disease	32	40		
Investigator: Not evaluable	13	20		
BICR: Objective response rate	195	30		
Investigator: Objective response rate	193	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point title	Duration of Response in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer

End point description:

Duration of Response (DoR) is defined as the date of the first documented objective response (complete response [CR] or partial response [PR]) to the first documented disease progression or death, whichever occurs first. DoR was based on blinded independent central review (BICR) and investigator assessment. Median was from Kaplan-Meier estimate. Confidence interval for median was computed using the Brookmeyer-Crowley method.

End point type	Secondary

End point timeframe:

From the date of the first documented objective response (CR or PR) to the first documented disease progression or death, whichever occurs first, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	163		
Units: months				
median (confidence interval 95%)				
BICR: DoR	10.7 (8.5 to 13.7)	6.8 (6.5 to 9.9)		
Investigator: DoR	8.3 (7.1 to 11.1)	5.6 (3.6 to 6.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Participants With HER2-low Breast Cancer (All Patients)

End point title	Duration of Response in Participants With HER2-low Breast Cancer (All Patients)

End point description:

Duration of Response (DoR) is defined as the date of the first documented objective response (complete response [CR] or partial response [PR]) to the first documented disease progression or death, whichever occurs first. DoR was based on blinded independent central review (BICR) and investigator assessment. Median was from Kaplan-Meier estimate. Confidence interval for median was computed using the Brookmeyer-Crowley method.

End point type	Secondary

End point timeframe:

From the date of the first documented objective response (CR or PR) to the first documented disease progression or death, whichever occurs first, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	184		
Units: months				
median (confidence interval 95%)				
BICR: DoR	10.7 (8.5 to 13.2)	6.8 (6.0 to 9.9)		
Investigator: DoR	8.3 (7.0 to 9.9)	5.6 (3.7 to 6.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Overall Survival Events (Deaths)

End point title	Number of Overall Survival Events (Deaths)

End point description:

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	184		
Units: events (deaths)				
number (not applicable)				
Overall survival events (deaths)	149	90		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: All-Cause Mortality

End point title	All-Cause Mortality

End point description:

All-cause mortality in the Safety Analysis Set is defined as all anticipated and unanticipated deaths due to any cause, with the number and frequency of such events by arm or comparison group of the clinical study.

End point type	Other pre-specified

End point timeframe:

From the date of randomization up to the date of death due to any cause, up to approximately 3 years

End point values	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	172		
Units: participants				
number (not applicable)				
All-cause mortality	148	88		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected from the date of main ICF up to 40 days (+7 days) after the last treatment, whether observed by the investigator or reported by the patient, up to approximately 3 years in the Safety Analysis Set.

Adverse event reporting additional description:

All-cause mortality was assessed in all randomized participants (Full Analysis Set). The other prespecified outcome measure reports all-cause mortality from the Safety Analysis Set (SAS). Other AEs and SAEs were assessed in the SAS. As prespecified, the Physician's Choice was based on the approved label per country and combined for analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Trastuzumab Deruxtecan (T-DXd)

Reporting group description:

Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to DS8201a with an initial dose of 5.4 mg/kg was infused for approximately 90 minutes. If there was no infusion-related reaction (IRR), doses of T-DXd after the initial dose of 5.4 mg/kg were infused for a minimum of 30 minutes.

Reporting group title	Physician's Choice

Reporting group description:

Participants with HER2-low, unresectable, and/or metastatic breast cancer who were previously treated with chemotherapy and randomized to a physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel, and nabpaclitaxel) in which the dose, regimen, administration, and dose modification followed the label approved in the country of drug administration or the National Comprehensive Cancer Network guidelines.

Serious adverse events	Trastuzumab Deruxtecan (T-DXd)	Physician's Choice	
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 371 (27.76%)	43 / 172 (25.00%)	
number of deaths (all causes)	149	90	
number of deaths resulting from adverse events	14	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			

subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 371 (0.27%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 371 (0.54%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Discomfort			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	2 / 371 (0.54%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Fatigue			
subjects affected / exposed	1 / 371 (0.27%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 371 (0.54%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (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 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	4 / 371 (1.08%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social problem			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 371 (1.35%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Haemoptysis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	7 / 371 (1.89%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 371 (0.81%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	7 / 371 (1.89%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 371 (0.54%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 371 (0.54%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical peritonitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 371 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	0 / 371 (0.00%)	3 / 172 (1.74%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 371 (0.00%)	5 / 172 (2.91%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 371 (0.27%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			

subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (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			
Epilepsy			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 371 (1.08%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 371 (1.08%)	4 / 172 (2.33%)	
occurrences causally related to treatment / all	1 / 4	3 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 371 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 371 (0.27%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			

subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (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	0 / 371 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			
subjects affected / exposed	3 / 371 (0.81%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 371 (1.08%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (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	4 / 371 (1.08%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 371 (0.54%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 371 (0.27%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hepatic function abnormal			
subjects affected / exposed	1 / 371 (0.27%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	2 / 371 (0.54%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 371 (0.54%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 371 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 371 (0.27%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 371 (0.81%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 371 (1.89%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	3 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 371 (1.35%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			

subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 371 (0.81%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 371 (0.54%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	4 / 371 (1.08%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 371 (0.27%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
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)	Physician's Choice	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	366 / 371 (98.65%)	167 / 172 (97.09%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	75 / 371 (20.22%)	43 / 172 (25.00%)	
occurrences (all)	107	58	
Aspartate aminotransferase increased			
subjects affected / exposed	92 / 371 (24.80%)	42 / 172 (24.42%)	
occurrences (all)	131	60	
Blood alkaline phosphatase increased			
subjects affected / exposed	36 / 371 (9.70%)	5 / 172 (2.91%)	
occurrences (all)	47	7	
Blood bilirubin increased			
subjects affected / exposed	25 / 371 (6.74%)	7 / 172 (4.07%)	
occurrences (all)	39	7	
Blood lactate dehydrogenase increased			
subjects affected / exposed	19 / 371 (5.12%)	9 / 172 (5.23%)	
occurrences (all)	32	14	
Gamma-glutamyltransferase increased			
subjects affected / exposed	20 / 371 (5.39%)	8 / 172 (4.65%)	
occurrences (all)	22	9	
Lymphocyte count decreased			
subjects affected / exposed	29 / 371 (7.82%)	12 / 172 (6.98%)	
occurrences (all)	68	16	
Neutrophil count decreased			
subjects affected / exposed	81 / 371 (21.83%)	61 / 172 (35.47%)	
occurrences (all)	195	145	

Platelet count decreased			
subjects affected / exposed	72 / 371 (19.41%)	12 / 172 (6.98%)	
occurrences (all)	129	25	
Weight decreased			
subjects affected / exposed	59 / 371 (15.90%)	14 / 172 (8.14%)	
occurrences (all)	61	15	
White blood cell count decreased			
subjects affected / exposed	78 / 371 (21.02%)	49 / 172 (28.49%)	
occurrences (all)	184	132	
Nervous system disorders			
Dizziness			
subjects affected / exposed	32 / 371 (8.63%)	9 / 172 (5.23%)	
occurrences (all)	43	11	
Dysgeusia			
subjects affected / exposed	37 / 371 (9.97%)	16 / 172 (9.30%)	
occurrences (all)	40	16	
Headache			
subjects affected / exposed	53 / 371 (14.29%)	11 / 172 (6.40%)	
occurrences (all)	74	13	
Neuropathy peripheral			
subjects affected / exposed	13 / 371 (3.50%)	16 / 172 (9.30%)	
occurrences (all)	13	17	
Paraesthesia			
subjects affected / exposed	8 / 371 (2.16%)	9 / 172 (5.23%)	
occurrences (all)	10	10	
Peripheral sensory neuropathy			
subjects affected / exposed	18 / 371 (4.85%)	19 / 172 (11.05%)	
occurrences (all)	19	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	137 / 371 (36.93%)	44 / 172 (25.58%)	
occurrences (all)	204	59	
Neutropenia			
subjects affected / exposed	49 / 371 (13.21%)	29 / 172 (16.86%)	
occurrences (all)	114	44	
Thrombocytopenia			

subjects affected / exposed	23 / 371 (6.20%)	4 / 172 (2.33%)	
occurrences (all)	31	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	69 / 371 (18.60%)	25 / 172 (14.53%)	
occurrences (all)	116	30	
Fatigue			
subjects affected / exposed	110 / 371 (29.65%)	49 / 172 (28.49%)	
occurrences (all)	154	58	
Malaise			
subjects affected / exposed	33 / 371 (8.89%)	10 / 172 (5.81%)	
occurrences (all)	60	10	
Oedema peripheral			
subjects affected / exposed	24 / 371 (6.47%)	10 / 172 (5.81%)	
occurrences (all)	25	15	
Pyrexia			
subjects affected / exposed	42 / 371 (11.32%)	22 / 172 (12.79%)	
occurrences (all)	51	33	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	20 / 371 (5.39%)	5 / 172 (2.91%)	
occurrences (all)	28	5	
Abdominal pain			
subjects affected / exposed	35 / 371 (9.43%)	8 / 172 (4.65%)	
occurrences (all)	47	8	
Abdominal pain upper			
subjects affected / exposed	31 / 371 (8.36%)	13 / 172 (7.56%)	
occurrences (all)	60	16	
Constipation			
subjects affected / exposed	124 / 371 (33.42%)	38 / 172 (22.09%)	
occurrences (all)	205	40	
Diarrhoea			
subjects affected / exposed	100 / 371 (26.95%)	38 / 172 (22.09%)	
occurrences (all)	179	52	
Dry mouth			

subjects affected / exposed	26 / 371 (7.01%)	9 / 172 (5.23%)	
occurrences (all)	28	9	
Dyspepsia			
subjects affected / exposed	34 / 371 (9.16%)	11 / 172 (6.40%)	
occurrences (all)	40	12	
Gastrooesophageal reflux disease			
subjects affected / exposed	23 / 371 (6.20%)	3 / 172 (1.74%)	
occurrences (all)	25	3	
Nausea			
subjects affected / exposed	281 / 371 (75.74%)	52 / 172 (30.23%)	
occurrences (all)	668	60	
Stomatitis			
subjects affected / exposed	41 / 371 (11.05%)	17 / 172 (9.88%)	
occurrences (all)	57	18	
Vomiting			
subjects affected / exposed	148 / 371 (39.89%)	23 / 172 (13.37%)	
occurrences (all)	365	27	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 371 (9.43%)	14 / 172 (8.14%)	
occurrences (all)	41	16	
Dyspnoea			
subjects affected / exposed	34 / 371 (9.16%)	14 / 172 (8.14%)	
occurrences (all)	40	16	
Epistaxis			
subjects affected / exposed	39 / 371 (10.51%)	2 / 172 (1.16%)	
occurrences (all)	46	2	
Pneumonitis			
subjects affected / exposed	21 / 371 (5.66%)	0 / 172 (0.00%)	
occurrences (all)	23	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	147 / 371 (39.62%)	57 / 172 (33.14%)	
occurrences (all)	153	59	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	5 / 371 (1.35%)	24 / 172 (13.95%)	
occurrences (all)	5	29	
Rash			
subjects affected / exposed	24 / 371 (6.47%)	9 / 172 (5.23%)	
occurrences (all)	27	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	24 / 371 (6.47%)	9 / 172 (5.23%)	
occurrences (all)	26	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	43 / 371 (11.59%)	20 / 172 (11.63%)	
occurrences (all)	56	25	
Back pain			
subjects affected / exposed	33 / 371 (8.89%)	10 / 172 (5.81%)	
occurrences (all)	42	12	
Myalgia			
subjects affected / exposed	22 / 371 (5.93%)	16 / 172 (9.30%)	
occurrences (all)	28	22	
Pain in extremity			
subjects affected / exposed	29 / 371 (7.82%)	5 / 172 (2.91%)	
occurrences (all)	39	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	27 / 371 (7.28%)	6 / 172 (3.49%)	
occurrences (all)	30	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	118 / 371 (31.81%)	33 / 172 (19.19%)	
occurrences (all)	217	39	
Hypoalbuminaemia			
subjects affected / exposed	32 / 371 (8.63%)	8 / 172 (4.65%)	
occurrences (all)	46	11	
Hypocalcaemia			
subjects affected / exposed	19 / 371 (5.12%)	5 / 172 (2.91%)	
occurrences (all)	23	7	

Hypokalaemia subjects affected / exposed occurrences (all)	38 / 371 (10.24%) 64	12 / 172 (6.98%) 16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2018	Updated inclusion/exclusion criteria, included definitions for assessments/efficacy outcomes, clarified timing of patient-reported outcome measures, and clarified pharmacokinetic procedures.
24 April 2019	Updated tissue biopsy procedures, number of study centers, clarified number of HR-negative and HR-postive patients to be enrolled, updated inclusion/exclusion criteria, and expanded medical history.
23 April 2020	Clarified dose regimen for Physician's Choice arm, added exploratory objective, updated inclusion/exclusion criteria, clarified statistical analysis and tumor assessments, revised study procedures (length of dose delay, withdrawal, screening, pregnancy testing, pharmacokinetic assessments), addressed utilization of patient-reported outcome measures.
12 October 2020	Addition of new timepoints for overall survival, progression-free survival added as an exploratory objective and endpoint, updated timing of primary analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported