Clinical trial results:
A Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a, an anti-HER2-antibody drug conjugate, versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pretreated with prior standard of care HER2 therapies, including T-DM1

Summary

EudraCT number	2018-000221-31
Trial protocol	GB BE CZ FR GR DE IT ES
Global end of trial date	

Results information

Result version number	v1
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification

Sponsor protocol code	DS8201-A-U301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03523585
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo
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	30 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 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 DS-8201a to investigator’s choice.

Protection of trial subjects:

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). The study protocol, amendments, the informed consent forms (ICF), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 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	United Kingdom: 35
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 57
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Brazil: 59
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Japan: 70
Country: Number of subjects enrolled	Korea, Republic of: 94
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Turkey: 52
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	608
EEA total number of subjects	230

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)	485
From 65 to 84 years	119
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 608 participants were enrolled at study sites in 15 countries. Primary results reported is from first participant randomized up to data cut-off date of 30 Jun 2022. The results presented are based on primary analysis up to 46 months.

Pre-assignment

Screening details:

Participants in The Physician's Choice (TPC) group were randomized to either trastuzumab/capecitabine or lapatinib/capecitabine. As prespecified, participants were assessed and reported separately per arm for the disposition, baseline characteristics, and safety tables. For efficacy assessments, all TPC participants were assessed together.

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 standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), 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
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Trastuzumab+Capecitabine

Arm description:

Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Trastuzumab/Capecitabine.

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Capecitabine 1250 mg/m2 administered orally (PO) twice daily approximately 12 hours apart (equivalent to 2500 mg/m2 total daily dose) on Days 1 to 14 of a 21-day (± 2 days) schedule

Investigational medicinal product name	Trastuzumab Deruxtecan
Investigational medicinal product code	
Other name	T-DXd
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Lapatinib+Capecitabine

Arm description:

Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Lapatinib/Capecitabine.

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Lapatinib 1250 mg PO daily on Days 1 to 21 of a 21-day (± 2 days) schedule

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Capecitabine 1250 mg/m2 administered orally (PO) twice daily approximately 12 hours apart (equivalent to 2500 mg/m2 total daily dose) on Days 1 to 14 of a 21-day (± 2 days) schedule

Number of subjects in period 1	Trastuzumab Deruxtecan (T-DXd)	Trastuzumab+Capecitabine	Lapatinib+Capecitabine
Started	406	91	111
Completed	94	1	4
Not completed	312	90	107
Clinical progression	23	5	10
Physician decision	2	1	-
Adverse event, non-fatal	74	5	9
Randomized but not treated	2	4	3
Death	4	-	1
Miscellaneous	1	-	-
Progressive disease	174	64	77
Lost to follow-up	1	-	-
Withdrawal by subject	30	11	6
Protocol deviation	1	-	1

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 standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), 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	Trastuzumab+Capecitabine
Reporting group description:	
Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Trastuzumab/Capecitabine.	
Reporting group title	Lapatinib+Capecitabine
Reporting group description:	
Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Lapatinib/Capecitabine.	

Reporting group values	Trastuzumab Deruxtecan (T-DXd)	Trastuzumab+Capecitabine	Lapatinib+Capecitabine
Number of subjects	406	91	111
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)	321	73	91
From 65-84 years	82	17	20
85 years and over	3	1	0
Age continuous Units: years			
arithmetic mean	54.6	55.7	54.6
standard deviation	± 11.99	± 11.40	± 11.06
Gender categorical Units: Subjects			
Female	403	89	111
Male	3	2	0

Reporting group values	Total		
Number of subjects	608		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	485		
From 65-84 years	119		
85 years and over	4		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	603		
Male	5		

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 standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), 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	Trastuzumab+Capecitabine
Reporting group description:	
Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Trastuzumab/Capecitabine.	
Reporting group title	Lapatinib+Capecitabine
Reporting group description:	
Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Lapatinib/Capecitabine.	
Subject analysis set title	The Physician's Choice (TPC)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patient's in Th Physician's Choice group were randomized to 1 of the following 2 regimens: trastuzumab/capecitabine or lapatinib/capecitabine.	

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

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 Participants Previously Treated With Trastuzumab Emtansine[1]
End point description:	
Progression-free survival (PFS) by BICR was defined as the time from the date of randomization 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.	
End point type	Primary
End point timeframe:	
Baseline up to 46 months postdose	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, participants were assessed and reported separately per comparator arm for the disposition, baseline characteristics, and safety tables. For efficacy assessments, all participants in the TPC group were combined and assessed together.

End point values	Trastuzumab Deruxtecan (T-DXd)	The Physician's Choice (TPC)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	406	202		
Units: months				
median (confidence interval 95%)				
Progression-free survival (PFS)	17.8 (14.3 to 20.8)	6.9 (5.5 to 8.4)		

Statistical analyses

Statistical analysis title	T-DXd vs TPC
Comparison groups	Trastuzumab Deruxtecan (T-DXd) v The Physician's Choice (TPC)
Number of subjects included in analysis	608
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [2]
Method	Stratified log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3589
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.284
upper limit	0.4535

Notes:

[2] - p value based on log-rank stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by IXRS

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

End point title	Overall Survival (OS) in Participants With HER2-positive, Unresectable and/or Metastatic Breast Cancer Participants Previously Treated With Trastuzumab Emtansine[3]

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 is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact
date at which the subject is known to be alive.

End point type	Secondary

End point timeframe:

Baseline up to 46 months postdose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, participants were assessed and reported separately per comparator arm for the disposition, baseline characteristics, and safety tables. For efficacy assessments, all participants in the TPC group were combined and assessed together.

End point values	Trastuzumab Deruxtecan (T-DXd)	The Physician's Choice (TPC)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	406[4]	202[5]		
Units: months				
median (confidence interval 95%)				
Overall survival (OS)	39.2 (32.7 to 9999)	26.5 (21.0 to 9999)		

Notes:

[4] - 9999=Upper limit of 95% CI was not estimable due to insufficient number of events

[5] - 9999=Upper limit of 95% CI was not estimable due to insufficient number of events

Statistical analyses

Statistical analysis title	T-DXd vs TPC
Comparison groups	Trastuzumab Deruxtecan (T-DXd) v The Physician's Choice (TPC)
Number of subjects included in analysis	608
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [6]
Method	Stratified log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6575
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5023
upper limit	0.8605

Notes:

[6] - p value based on log-rank stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by IXRS

Secondary: Percentage of Patients With Objective Response Rate (ORR) in Participants With HER2-positive, Unresectable and/ or Metastatic Breast Cancer Participants Previously Treated With Trastuzumab Emtansine

End point title	Percentage of Patients With Objective Response Rate (ORR) in Participants With HER2-positive, Unresectable and/ or Metastatic Breast Cancer Participants Previously Treated With Trastuzumab Emtansine[7]

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 based on BICR and Investigator Assessment is reported.

End point type	Secondary

End point timeframe:

Baseline up to 46 months postdose

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, participants were assessed and reported separately per comparator arm for the disposition, baseline characteristics, and safety tables. For efficacy assessments, all participants in the TPC group were combined and assessed together.

End point values	Trastuzumab Deruxtecan (T-DXd)	The Physician's Choice (TPC)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	406	202		
Units: percentage of patients				
number (confidence interval 95%)				
BICR	69.7 (65.0 to 74.1)	29.2 (23.0 to 36.0)		
Investigator Assessment	74.1 (69.6 to 78.3)	26.7 (20.8 to 33.4)		

Statistical analyses

Statistical analysis title	T-DXd vs TPC; BICR
Comparison groups	Trastuzumab Deruxtecan (T-DXd) v The Physician's Choice (TPC)
Number of subjects included in analysis	608
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[8] - Cochran-Mantel-Haenszel test adjusted for stratification factors: hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by the IXRS.

Statistical analysis title	T-DXd vs TPC; Investigator Assessment
Comparison groups	Trastuzumab Deruxtecan (T-DXd) v The Physician's Choice (TPC)
Number of subjects included in analysis	608
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel

Notes:

[9] - Cochran-Mantel-Haenszel test adjusted for stratification factors: hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by the IXRS.

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

End point title	Duration of Response (DoR) Based on BICR in Participants With HER2-positive, Unresectable and/or Metastatic Breast Cancer Participants Previously Treated With Trastuzumab Emtansine[10]

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.

End point type	Secondary

End point timeframe:

Baseline up to 46 months postdose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, participants were assessed and reported separately per comparator arm for the disposition, baseline characteristics, and safety tables. For efficacy assessments, all participants in the TPC group were combined and assessed together.

End point values	Trastuzumab Deruxtecan (T-DXd)	The Physician's Choice (TPC)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	283[11]	59		
Units: months				
median (confidence interval 95%)				
Duration of response (DoR)	19.6 (15.9 to 9999)	8.3 (5.8 to 9.5)		

Notes:

[11] - 9999=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 Participants Previously Treated With Trastuzumab Emtansine

End point title	Progression-Free Survival (PFS) Based on Investigator Assessment in Participants With HER2-positive, Unresectable and/or Metastatic Breast Cancer Participants Previously Treated With Trastuzumab Emtansine[12]

End point description:

Progression-free survival (PFS) by investigator assessment was defined as the time from the date of randomization 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.

End point type	Secondary

End point timeframe:

Up to 46 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, participants were assessed and reported separately per comparator arm for the disposition, baseline characteristics, and safety tables. For efficacy assessments, all participants in the TPC group were combined and assessed together.

End point values	Trastuzumab Deruxtecan (T-DXd)	The Physician's Choice (TPC)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	406	202		
Units: months				
median (confidence interval 95%)				
Progression-free survival (PFS); Investigator	16.7 (14.3 to 19.6)	5.5 (4.4 to 7.0)		

Statistical analyses

Statistical analysis title	T-DXd vs TPC; Investigator Assessment
Comparison groups	Trastuzumab Deruxtecan (T-DXd) v The Physician's Choice (TPC)
Number of subjects included in analysis	608
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [13]
Method	Stratified log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.2828
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.227
upper limit	0.3524

Notes:

[13] - p value based on log-rank stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by IXRS

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 46 months.

Adverse event reporting additional description:

A TEAE is an AE that occurs, having been absent before the first dose, or has worsened in severity or seriousness after the initiating the study drug until 47 days after last dose. AEs were assessed in the SAS at data cutoff date of 30 Jun 2022. All-Cause Mortality was analyzed in the FAS. Serious and Other AEs were analyzed in the SAS.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

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 standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), 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	Trastuzumab+Capecitabine

Reporting group description:

Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Trastuzumab/Capecitabine.

Reporting group title	Lapatinib+Capecitabine

Reporting group description:

Participants with HER2 positive, unresectable and/or metastatic breast cancer participants previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1), who received investigator's choice treatment, Lapatinib/Capecitabine.

Serious adverse events	Trastuzumab Deruxtecan (T-DXd)	Trastuzumab+Capecitabine	Lapatinib+Capecitabine
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 404 (25.50%)	19 / 87 (21.84%)	27 / 108 (25.00%)
number of deaths (all causes)	143	40	46
number of deaths resulting from adverse events	11	1	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to ovary			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tumour thrombotic microangiopathy			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Brachiocephalic vein thrombosis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	1 / 404 (0.25%)	1 / 87 (1.15%)	3 / 108 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Fatigue			

subjects affected / exposed	3 / 404 (0.74%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 404 (0.74%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Interstitial lung disease			
subjects affected / exposed	3 / 404 (0.74%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal haemorrhage			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 404 (0.50%)	1 / 87 (1.15%)	3 / 108 (2.78%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	10 / 404 (2.48%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	11 / 11	0 / 0	0 / 1
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			

subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic enzymes increased			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Craniocerebral injury			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation necrosis			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune thyroiditis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopat			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral ischaemia			

subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoplegia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasogenic cerebral oedema			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 404 (0.99%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Scleritis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 404 (0.50%)	3 / 87 (3.45%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 404 (0.74%)	3 / 87 (3.45%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	2 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric antral vascular ectasia			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	5 / 404 (1.24%)	2 / 87 (2.30%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	6 / 404 (1.49%)	2 / 87 (2.30%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis haemorrhagic			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			

subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	11 / 404 (2.72%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 404 (0.25%)	1 / 87 (1.15%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingivitis			
subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	0 / 404 (0.00%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 404 (1.49%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 404 (0.00%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 404 (0.25%)	1 / 87 (1.15%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 404 (0.99%)	0 / 87 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Trastuzumab Deruxtecan (T-DXd)	Trastuzumab+Capecitabine	Lapatinib+Capecitabine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	404 / 404 (100.00%)	87 / 87 (100.00%)	108 / 108 (100.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	61 / 404 (15.10%)	6 / 87 (6.90%)	14 / 108 (12.96%)
occurrences (all)	96	6	15
Aspartate aminotransferase increased			
subjects affected / exposed	66 / 404 (16.34%)	5 / 87 (5.75%)	18 / 108 (16.67%)
occurrences (all)	103	8	20
Blood alkaline phosphatase increased			
subjects affected / exposed	24 / 404 (5.94%)	4 / 87 (4.60%)	4 / 108 (3.70%)
occurrences (all)	30	4	4
Blood bilirubin increased			
subjects affected / exposed	20 / 404 (4.95%)	4 / 87 (4.60%)	17 / 108 (15.74%)
occurrences (all)	26	5	29
Lymphocyte count decreased			
subjects affected / exposed	30 / 404 (7.43%)	2 / 87 (2.30%)	2 / 108 (1.85%)
occurrences (all)	46	3	2
Neutrophil count decreased			
subjects affected / exposed	79 / 404 (19.55%)	7 / 87 (8.05%)	7 / 108 (6.48%)
occurrences (all)	227	8	15
Platelet count decreased			
subjects affected / exposed	49 / 404 (12.13%)	5 / 87 (5.75%)	7 / 108 (6.48%)
occurrences (all)	92	7	7
Weight decreased			
subjects affected / exposed	71 / 404 (17.57%)	2 / 87 (2.30%)	5 / 108 (4.63%)
occurrences (all)	74	2	5
White blood cell count decreased			
subjects affected / exposed	59 / 404 (14.60%)	5 / 87 (5.75%)	4 / 108 (3.70%)
occurrences (all)	145	10	10
Nervous system disorders			

Dizziness			
subjects affected / exposed	32 / 404 (7.92%)	5 / 87 (5.75%)	9 / 108 (8.33%)
occurrences (all)	38	5	11
Dysgeusia			
subjects affected / exposed	33 / 404 (8.17%)	3 / 87 (3.45%)	1 / 108 (0.93%)
occurrences (all)	35	3	1
Headache			
subjects affected / exposed	79 / 404 (19.55%)	7 / 87 (8.05%)	5 / 108 (4.63%)
occurrences (all)	116	8	5
Neuropathy peripheral			
subjects affected / exposed	12 / 404 (2.97%)	6 / 87 (6.90%)	4 / 108 (3.70%)
occurrences (all)	15	6	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	114 / 404 (28.22%)	13 / 87 (14.94%)	13 / 108 (12.04%)
occurrences (all)	203	15	14
Leukopenia			
subjects affected / exposed	23 / 404 (5.69%)	2 / 87 (2.30%)	2 / 108 (1.85%)
occurrences (all)	41	2	2
Lymphopenia			
subjects affected / exposed	21 / 404 (5.20%)	1 / 87 (1.15%)	1 / 108 (0.93%)
occurrences (all)	43	1	1
Neutropenia			
subjects affected / exposed	65 / 404 (16.09%)	4 / 87 (4.60%)	6 / 108 (5.56%)
occurrences (all)	138	4	10
Thrombocytopenia			
subjects affected / exposed	41 / 404 (10.15%)	4 / 87 (4.60%)	7 / 108 (6.48%)
occurrences (all)	68	7	15
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	97 / 404 (24.01%)	6 / 87 (6.90%)	13 / 108 (12.04%)
occurrences (all)	179	9	13
Fatigue			
subjects affected / exposed	144 / 404 (35.64%)	20 / 87 (22.99%)	32 / 108 (29.63%)
occurrences (all)	223	23	40
Mucosal inflammation			

subjects affected / exposed	15 / 404 (3.71%)	6 / 87 (6.90%)	9 / 108 (8.33%)
occurrences (all)	22	7	10
Oedema peripheral			
subjects affected / exposed	27 / 404 (6.68%)	4 / 87 (4.60%)	5 / 108 (4.63%)
occurrences (all)	37	4	5
Pyrexia			
subjects affected / exposed	51 / 404 (12.62%)	5 / 87 (5.75%)	7 / 108 (6.48%)
occurrences (all)	68	5	8
Eye disorders			
Dry eye			
subjects affected / exposed	23 / 404 (5.69%)	4 / 87 (4.60%)	5 / 108 (4.63%)
occurrences (all)	24	4	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	45 / 404 (11.14%)	7 / 87 (8.05%)	11 / 108 (10.19%)
occurrences (all)	63	9	13
Abdominal pain upper			
subjects affected / exposed	38 / 404 (9.41%)	7 / 87 (8.05%)	11 / 108 (10.19%)
occurrences (all)	82	7	14
Constipation			
subjects affected / exposed	142 / 404 (35.15%)	12 / 87 (13.79%)	9 / 108 (8.33%)
occurrences (all)	194	13	12
Diarrhoea			
subjects affected / exposed	109 / 404 (26.98%)	33 / 87 (37.93%)	69 / 108 (63.89%)
occurrences (all)	216	44	156
Dyspepsia			
subjects affected / exposed	48 / 404 (11.88%)	6 / 87 (6.90%)	12 / 108 (11.11%)
occurrences (all)	62	6	12
Nausea			
subjects affected / exposed	292 / 404 (72.28%)	29 / 87 (33.33%)	44 / 108 (40.74%)
occurrences (all)	790	34	54
Stomatitis			
subjects affected / exposed	44 / 404 (10.89%)	11 / 87 (12.64%)	25 / 108 (23.15%)
occurrences (all)	59	14	28
Vomiting			

subjects affected / exposed	150 / 404 (37.13%)	9 / 87 (10.34%)	14 / 108 (12.96%)
occurrences (all)	335	12	22
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	53 / 404 (13.12%)	7 / 87 (8.05%)	13 / 108 (12.04%)
occurrences (all)	67	8	14
Dyspnoea			
subjects affected / exposed	33 / 404 (8.17%)	3 / 87 (3.45%)	10 / 108 (9.26%)
occurrences (all)	39	3	13
Epistaxis			
subjects affected / exposed	33 / 404 (8.17%)	5 / 87 (5.75%)	7 / 108 (6.48%)
occurrences (all)	39	5	8
Pneumonitis			
subjects affected / exposed	25 / 404 (6.19%)	0 / 87 (0.00%)	0 / 108 (0.00%)
occurrences (all)	25	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	150 / 404 (37.13%)	4 / 87 (4.60%)	4 / 108 (3.70%)
occurrences (all)	165	4	4
Dermatitis acneiform			
subjects affected / exposed	2 / 404 (0.50%)	0 / 87 (0.00%)	10 / 108 (9.26%)
occurrences (all)	2	0	15
Dry skin			
subjects affected / exposed	11 / 404 (2.72%)	3 / 87 (3.45%)	6 / 108 (5.56%)
occurrences (all)	11	3	6
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 404 (1.73%)	48 / 87 (55.17%)	52 / 108 (48.15%)
occurrences (all)	9	66	64
Pruritus			
subjects affected / exposed	22 / 404 (5.45%)	2 / 87 (2.30%)	6 / 108 (5.56%)
occurrences (all)	26	2	6
Rash			
subjects affected / exposed	27 / 404 (6.68%)	3 / 87 (3.45%)	19 / 108 (17.59%)
occurrences (all)	28	4	21
Rash maculo-papular			

subjects affected / exposed	6 / 404 (1.49%)	2 / 87 (2.30%)	6 / 108 (5.56%)
occurrences (all)	7	3	6
Skin toxicity			
subjects affected / exposed	1 / 404 (0.25%)	1 / 87 (1.15%)	6 / 108 (5.56%)
occurrences (all)	1	1	8
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 404 (6.19%)	6 / 87 (6.90%)	5 / 108 (4.63%)
occurrences (all)	27	6	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	42 / 404 (10.40%)	7 / 87 (8.05%)	7 / 108 (6.48%)
occurrences (all)	56	7	7
Back pain			
subjects affected / exposed	36 / 404 (8.91%)	1 / 87 (1.15%)	5 / 108 (4.63%)
occurrences (all)	38	1	5
Muscle spasms			
subjects affected / exposed	13 / 404 (3.22%)	4 / 87 (4.60%)	7 / 108 (6.48%)
occurrences (all)	22	4	7
Myalgia			
subjects affected / exposed	23 / 404 (5.69%)	4 / 87 (4.60%)	4 / 108 (3.70%)
occurrences (all)	37	4	4
Pain in extremity			
subjects affected / exposed	24 / 404 (5.94%)	4 / 87 (4.60%)	4 / 108 (3.70%)
occurrences (all)	30	5	4
Infections and infestations			
COVID-19			
subjects affected / exposed	47 / 404 (11.63%)	1 / 87 (1.15%)	2 / 108 (1.85%)
occurrences (all)	52	1	2
Nasopharyngitis			
subjects affected / exposed	21 / 404 (5.20%)	3 / 87 (3.45%)	2 / 108 (1.85%)
occurrences (all)	25	3	2
Paronychia			
subjects affected / exposed	10 / 404 (2.48%)	3 / 87 (3.45%)	11 / 108 (10.19%)
occurrences (all)	12	4	20
Upper respiratory tract infection			

subjects affected / exposed	21 / 404 (5.20%)	3 / 87 (3.45%)	3 / 108 (2.78%)
occurrences (all)	25	3	3
Urinary tract infection			
subjects affected / exposed	34 / 404 (8.42%)	3 / 87 (3.45%)	3 / 108 (2.78%)
occurrences (all)	58	3	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	124 / 404 (30.69%)	15 / 87 (17.24%)	20 / 108 (18.52%)
occurrences (all)	171	16	25
Hypokalaemia			
subjects affected / exposed	28 / 404 (6.93%)	7 / 87 (8.05%)	6 / 108 (5.56%)
occurrences (all)	40	8	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2018	Updated the starting dose of T-DXd to 5.4 mg/kg, clarified if study treatment was delayed more than 4 weeks from the planned date of administration, the subject was withdrawn from study drug, removed stipulation that Sponsor was to provide all TPC medication, clarified that if archived tissue was not available, a fresh biopsy was required, and updated inclusion and exclusion criteria
08 March 2019	Clarified that complete and partial responses included confirmation of response and that the related objectives and endpoints were to use confirmed responses, clarified that for the TPC arm administration, dose adjustments, prohibited medication, and monitoring were to follow the locally approved label, clarified that secondary analyses were to be performed at the time of primary PFS analysis, updated CBR from a secondary objective/endpoint to be an exploratory objective/endpoint, and updated inclusion and exclusion criteria
26 April 2019	Updated the ILD monitoring plan and ILD dose modification guidelines to clarify that study drug could be interrupted for any ILD event and that subjects with an ILD event of CTCAE Grade 2, 3 or 4 be permanently discontinued from study drug
23 April 2020	Added an interim analysis that allowed for an earlier evaluation of OS to coincide with the PFS analysis, updated the secondary objective and endpoint of OS to be a key secondary efficacy objective and endpoint, updated the intent-to-treat analysis set to be the FAS, added an appendix with instructions related to COVID-19 including prohibiting the use of chloroquine and hydroxychloroquine during the treatment period and instituting a washout period, clarified that tumor assessments were conducted every 6 weeks from randomization and were performed while the subject remained on study until progression of disease, withdrawal of consent, death, or loss to follow-up, updated inclusion and exclusion criteria, and updated LVEF monitoring and ILD monitoring and management guidelines
05 August 2020	Added biomarker analyses to evaluate the impact of the global pandemic caused by COVID-19 at the subject-level and study-level, revised exploratory endpoints to include evaluation of PFS2 and added the corresponding analysis as well as clarifying the withdrawal of consent language, and updated inclusion and exclusion criteria
17 March 2022	Introduced alterative timing for the primary endpoint and an additional time-based condition to conduct the primary analysis was added and defined the end-of-study hypothesis testing period and study closure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported