Clinical trial results:
A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Patients with HER2+ Metastatic Breast Cancer Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment.

Summary

EudraCT number	2015-000380-13
Trial protocol	BE DE PT CZ AT FI ES DK FR PL IT
Global end of trial date	14 June 2022

Results information

Result version number	v1 (current)
This version publication date	18 June 2023
First version publication date	18 June 2023

Trial information

Trial identification

Sponsor protocol code	CP-MGAH22-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02492711
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MacroGenics, Inc
Sponsor organisation address	9704 Medical Center Dr., Rockville, United States, 20850
Public contact	Global Trial Manager, MacroGenics, Inc., 001 3012515172, info@macrogenics.com
Scientific contact	Global Trial Manager, MacroGenics, Inc., 001 3012515172, info@macrogenics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy, as measured by progression-free survival (PFS) assessed by independent review and overall survival (OS), of margetuximab plus chemotherapy compared with trastuzumab plus chemotherapy in patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of antiHER2 directed therapy in the metastatic setting, and who have received at least one, and no more than three, lines of therapy overall in the metastatic setting.

Protection of trial subjects:

The trial was designed, conducted, and monitored in accordance with ethical principles that have their origin in the Declaration of Helsinki and in compliance with Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with all national and local laws and regulations of countries in which the trial was performed.

Background therapy:

Physician's choice of chemotherapy - Capecitabine (Xeloda®):1000 mg/m2 BID for 14 days in a 21-day cycle, or Eribulin (Halaven®): 1.4 mg/m2 on days 1 and 8 of a 21-day cycle, or Gemcitabine (Gemzar®): 1000 mg/m2 on days 1 and 8 of a 21-day cycle, or Vinorelbine (Navelbine®): 25-30 mg/m2 on days 1 and 8 of a 21-day cycle

Evidence for comparator: -

Actual start date of recruitment	15 July 2015
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	Netherlands: 7
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Spain: 61
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 40

Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 89
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Puerto Rico: 4
Country: Number of subjects enrolled	United States: 218
Worldwide total number of subjects	624
EEA total number of subjects	304

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)	490
From 65 to 84 years	132
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Before randomization, Investigators selected 1 of 4 chemotherapy agents (capecitabine, eribulin, gemcitabine, or vinorelbine) for each subject. Subjects were then randomized 1:1 to receive either margetuximab or trastuzumab with the selected chemotherapy. An non-randomized cohort was later added to evaluate lower infusion duration of margetuximab.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Margetuximab Plus Chemotherapy

Arm description:

Margetuximab 15 mg/kg administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens

Arm type	Experimental
Investigational medicinal product name	margetuximab
Investigational medicinal product code	
Other name	MGAH22
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Margetuximab 15 mg/kg administered every 21 days

Arm title	Trastuzumab Plus Chemotherapy

Arm description:

Trastuzumab administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens

Arm type	Active comparator
Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab 8 mg/kg initial dose then 6 mg/kg given every 21 days

Arm title	Margetuximab Infusion Substudy

Arm description:

Margetuximab with or without chemotherapy administered as a 120 minute first infusion in Cycle 1 followed by 60-minute or 30-minute infusion in Cycle 2

Arm type	Experimental

Investigational medicinal product name	margetuximab
Investigational medicinal product code	
Other name	MGAH22
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Margetuximab 15 mg/kg administered every 21 days, as a 120 minute first infusion in Cycle 1 followed by 60-minute or 30-minute infusion in Cycle 2

Number of subjects in period 1	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy	Margetuximab Infusion Substudy
Started	266	270	88
Completed	230	230	75
Not completed	36	40	13
Consent withdrawn by subject	10	16	5
Physician decision	10	6	4
Adverse event, non-fatal	9	9	2
Death	3	3	-
Other	-	-	1
Study treatment delay	2	1	-
Never treated	2	4	-
Lost to follow-up	-	-	1
Change in chemotherapy	-	1	-

Period 2

Period 2 title	Infusion Sub-Study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Margetuximab Stage A1

Arm description:

Margetuximab administered as a 120 minute first infusion in Cycle 1 followed by 60 minute infusion in Cycle 2

Arm type	Experimental
Investigational medicinal product name	margetuximab
Investigational medicinal product code	
Other name	MGAH22
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Margetuximab 15 mg/kg administered every 21 days

Arm title	Margetuximab Stage A2

Arm description:

Margetuximab administered as a 120 minute first infusion in Cycle 1 followed by 30 minute infusion in Cycle 2

Arm type	Experimental
Investigational medicinal product name	margetuximab
Investigational medicinal product code	
Other name	MGAH22
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Margetuximab 15 mg/kg administered every 21 days

Arm title	Margetuximab Stage B

Arm description:

Margetuximab administered as a 120 minute first infusion in Cycle 1 followed by 30 minute infusion in Cycle 2

Arm type	Experimental
Investigational medicinal product name	margetuximab
Investigational medicinal product code	
Other name	MGAH22
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Margetuximab 15 mg/kg administered every 21 days

Number of subjects in period 2[1]	Margetuximab Stage A1	Margetuximab Stage A2	Margetuximab Stage B
Started	8	9	71
Completed	8	9	71

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Period 2 consists of an additional non-randomized cohort that evaluated lower infusion duration of margetuximab. This period is separate from the preceding period.

Baseline characteristics

Reporting groups	
Reporting group title	Margetuximab Plus Chemotherapy
Reporting group description:	
Margetuximab 15 mg/kg administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens	
Reporting group title	Trastuzumab Plus Chemotherapy
Reporting group description:	
Trastuzumab administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens	
Reporting group title	Margetuximab Infusion Substudy
Reporting group description:	
Margetuximab with or without chemotherapy administered as a 120 minute first infusion in Cycle 1 followed by 60-minute or 30-minute infusion in Cycle 2	

Reporting group values	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy	Margetuximab Infusion Substudy
Number of subjects	266	270	88
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	54.4	55.7	54.5
standard deviation	± 11.4	± 11.5	± 12.5
Gender categorical			
Units: Subjects			
Female	266	267	87
Male	0	3	1

Reporting group values	Total		
Number of subjects	624		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	620		
Male	4		

End points

End points reporting groups

Reporting group title	Margetuximab Plus Chemotherapy
Reporting group description:	
Margetuximab 15 mg/kg administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens	
Reporting group title	Trastuzumab Plus Chemotherapy
Reporting group description:	
Trastuzumab administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens	
Reporting group title	Margetuximab Infusion Substudy
Reporting group description:	
Margetuximab with or without chemotherapy administered as a 120 minute first infusion in Cycle 1 followed by 60-minute or 30-minute infusion in Cycle 2	
Reporting group title	Margetuximab Stage A1
Reporting group description:	
Margetuximab administered as a 120 minute first infusion in Cycle 1 followed by 60 minute infusion in Cycle 2	
Reporting group title	Margetuximab Stage A2
Reporting group description:	
Margetuximab administered as a 120 minute first infusion in Cycle 1 followed by 30 minute infusion in Cycle 2	
Reporting group title	Margetuximab Stage B
Reporting group description:	
Margetuximab administered as a 120 minute first infusion in Cycle 1 followed by 30 minute infusion in Cycle 2	

Primary: Progression-free Survival (PFS) as Determined by Independent Radiological Review.

End point title	Progression-free Survival (PFS) as Determined by Independent Radiological Review.[1]
End point description:	
PFS is measured from the time of randomization until first documented disease progression or death from any cause, whichever is first.	
End point type	Primary
End point timeframe:	
Tumor assessments are conducted every 6 weeks for the first 24 weeks and then every 24 weeks until progression of cancer, average 5 months.	

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: This endpoint is not relevant to the infusion sub-study arm.

End point values	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	270		
Units: months				
median (confidence interval 95%)	5.8 (5.52 to 6.97)	4.9 (4.17 to 5.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Stratified Cox Proportional Model	
Comparison groups	Trastuzumab Plus Chemotherapy v Margetuximab Plus Chemotherapy
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0334
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.593
upper limit	0.979

Primary: Overall Survival (OS) Defined as the Number of Days From Randomization to the Date of Death (From Any Cause)

End point title	Overall Survival (OS) Defined as the Number of Days From Randomization to the Date of Death (From Any Cause)[2]
End point description: Overall survival is the time from randomization until death from any cause	
End point type	Primary
End point timeframe: Throughout the study, average 21 months	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is not relevant to the infusion sub-study arm.

End point values	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	270		
Units: months				
median (confidence interval 95%)	21.6 (0.66 to 61.44)	21.9 (0.07 to 64.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Stratified Cox Proportional Model	
Comparison groups	Trastuzumab Plus Chemotherapy v Margetuximab Plus Chemotherapy
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6204 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.774
upper limit	1.165

Notes:

[3] - Stratified Log-Rank Test

Primary: Number of Patients With Grade 3 or Higher Infusion Related Reactions

End point title	Number of Patients With Grade 3 or Higher Infusion Related Reactions[4]
End point description:	
Incidence of Grade 3 or higher infusion-related reactions for patients receiving 60-minute or 30-minute infusions of margetuximab in Cycle 2 of treatment	
End point type	Primary
End point timeframe:	
22 days	

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was specific to the infusion substudy arm only.

End point values	Margetuximab Stage A1	Margetuximab Stage A2	Margetuximab Stage B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	71	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS), as Assessed by Study Investigators.

End point title	Progression-free Survival (PFS), as Assessed by Study Investigators.[5]

End point description:

End point type	Secondary

End point timeframe:

Tumor assessments are conducted every 6 weeks for the first 24 weeks and then every 24 weeks until progression of cancer, up to 6.5 years

Notes:

[5] - 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: This endpoint is not relevant to the infusion sub-study arm.

End point values	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	177		
Units: months				
median (confidence interval 95%)	5.6 (5.06 to 6.67)	4.2 (3.98 to 5.39)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Stratified Cox Proportional Model	
Comparison groups	Margetuximab Plus Chemotherapy v Trastuzumab Plus Chemotherapy
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.556
upper limit	0.87

Notes:

[6] - Stratified Log-Rank Test

Secondary: Objective Response Rate (ORR) as Determined by Independent Radiological Review

End point title	Objective Response Rate (ORR) as Determined by Independent Radiological Review[7]

End point description:

Objective response rate includes all patients with either a complete response (CR) or a partial response (PR) to study treatment

End point type	Secondary

End point timeframe:

Tumor assessments are conducted every 6 weeks for the first 24 weeks and then every 24 weeks until progression of cancer, up to 6.5 years

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: This endpoint is not relevant to the infusion sub-study arm.

End point values	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	262		
Units: Participants				
CR	7	4		
PR	51	38		
No response, PD, not evaluable or not available	204	220		

Statistical analyses

No statistical analyses for this end point

Secondary: Infusion Rate Sub-study All Safety

End point title	Infusion Rate Sub-study All Safety

End point description:

Incidence of all grades of infusion-related reactions

End point type	Secondary

End point timeframe:

Throughout the study, average duration 6 months

End point values	Margetuximab Stage A1	Margetuximab Stage A2	Margetuximab Stage B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	71	
Units: Participants				
Infusion related reaction Cycle 1	1	1	16	
Infusion related reaction Cycle 2 or higher	0	0	2	
No infusion related reaction	7	8	55	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the time of first dose through 30 days after the last dose, average 6 months. All-cause mortality was collected from the first dose until the primary completion date, average 2 years.

Adverse event reporting additional description:

AEs are based on physical exam, patient reports, and significant abnormal laboratory values. AEs were not collected in survival follow up. Only SAEs were collected in survival follow up if related to study treatment. Only patients who received study treatments were assessed for safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.10

Reporting groups

Reporting group title	Margetuximab Plus Chemotherapy

Reporting group description:

Margetuximab administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens.

Reporting group title	Trastuzumab Plus Chemotherapy

Reporting group description:

Trastuzumab administered every 21 days with physician's choice of 1 of 4 backbone chemotherapy regimens

Reporting group title	Margetuximab Infusion Substudy

Reporting group description:

Margetuximab with or without chemotherapy

Serious adverse events	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy	Margetuximab Infusion Substudy
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 264 (17.80%)	51 / 266 (19.17%)	17 / 88 (19.32%)
number of deaths (all causes)	204	202	62
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Metastases to bone			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Vascular disorders			

Embolism			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Haematoma			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Subclavian vein thrombosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Vasculitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 264 (0.76%)	3 / 266 (1.13%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 264 (0.38%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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

Chills			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Death			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Infusion site extravasation			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Pain			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic oedema			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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			
Pleural effusion			
subjects affected / exposed	1 / 264 (0.38%)	4 / 266 (1.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 264 (0.38%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumothorax			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	1 / 88 (1.14%)
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	2 / 264 (0.76%)	0 / 266 (0.00%)	0 / 88 (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
Dyspnoea			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Pneumothorax spontaneous			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Pulmonary oedema			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 264 (0.38%)	1 / 266 (0.38%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			

subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 264 (1.14%)	0 / 266 (0.00%)	0 / 88 (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
Ankle fracture			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Femoral neck fracture			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Procedural haemorrhage			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Subdural haematoma			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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

Atrial fibrillation			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Ventricular tachycardia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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 intracranial			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Headache			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Loss of consciousness			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	4 / 264 (1.52%)	10 / 266 (3.76%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 4	2 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	2 / 264 (0.76%)	2 / 266 (0.75%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 264 (1.52%)	1 / 266 (0.38%)	0 / 88 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 264 (0.38%)	1 / 266 (0.38%)	2 / 88 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 264 (0.38%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Dysphagia			

subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Impaired gastric emptying			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Intestinal obstruction			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Irritable bowel syndrome			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Large intestine perforation			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Small intestinal obstruction			

subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Pathological fracture			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Spondylolisthesis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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			
Pneumonia			
subjects affected / exposed	4 / 264 (1.52%)	8 / 266 (3.01%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 4	1 / 8	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Cellulitis			
subjects affected / exposed	1 / 264 (0.38%)	3 / 266 (1.13%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 264 (0.76%)	2 / 266 (0.75%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 264 (0.38%)	2 / 266 (0.75%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 264 (0.00%)	2 / 266 (0.75%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acinetobacter infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			

subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Catheter site infection			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Coronavirus infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Device related infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Device related sepsis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Gastroenteritis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Infected bite			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Infection			

subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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 infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Mastoiditis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Periorbital cellulitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Pseudomonal sepsis			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 264 (0.00%)	0 / 266 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Soft tissue infection			

subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Streptococcal bacteraemia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 264 (0.00%)	1 / 266 (0.38%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Hypoglycaemia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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
Hypovolaemia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 266 (0.00%)	0 / 88 (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

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

Non-serious adverse events	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy	Margetuximab Infusion Substudy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	213 / 264 (80.68%)	210 / 266 (78.95%)	68 / 88 (77.27%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	32 / 264 (12.12%)	38 / 266 (14.29%)	12 / 88 (13.64%)
occurrences (all)	99	90	26
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 264 (8.33%)	34 / 266 (12.78%)	12 / 88 (13.64%)
occurrences (all)	41	57	30
Alanine aminotransferase increased			
subjects affected / exposed	26 / 264 (9.85%)	26 / 266 (9.77%)	11 / 88 (12.50%)
occurrences (all)	49	61	24
White blood cell count decreased			
subjects affected / exposed	20 / 264 (7.58%)	26 / 266 (9.77%)	8 / 88 (9.09%)
occurrences (all)	73	60	15
Weight decreased			
subjects affected / exposed	16 / 264 (6.06%)	15 / 266 (5.64%)	9 / 88 (10.23%)
occurrences (all)	17	19	11
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	33 / 264 (12.50%)	9 / 266 (3.38%)	18 / 88 (20.45%)
occurrences (all)	36	15	52
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 264 (18.94%)	43 / 266 (16.17%)	11 / 88 (12.50%)
occurrences (all)	82	89	14
Neuropathy peripheral			
subjects affected / exposed	26 / 264 (9.85%)	28 / 266 (10.53%)	7 / 88 (7.95%)
occurrences (all)	36	38	8
Dizziness			
subjects affected / exposed	26 / 264 (9.85%)	17 / 266 (6.39%)	5 / 88 (5.68%)
occurrences (all)	31	20	6

Dysgeusia			
subjects affected / exposed	16 / 264 (6.06%)	15 / 266 (5.64%)	7 / 88 (7.95%)
occurrences (all)	17	17	7
Peripheral sensory neuropathy			
subjects affected / exposed	17 / 264 (6.44%)	13 / 266 (4.89%)	3 / 88 (3.41%)
occurrences (all)	28	23	4
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	72 / 264 (27.27%)	54 / 266 (20.30%)	17 / 88 (19.32%)
occurrences (all)	257	154	45
Anaemia			
subjects affected / exposed	48 / 264 (18.18%)	61 / 266 (22.93%)	18 / 88 (20.45%)
occurrences (all)	100	126	42
Thrombocytopenia			
subjects affected / exposed	22 / 264 (8.33%)	13 / 266 (4.89%)	3 / 88 (3.41%)
occurrences (all)	35	24	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	112 / 264 (42.42%)	95 / 266 (35.71%)	24 / 88 (27.27%)
occurrences (all)	187	144	33
Pyrexia			
subjects affected / exposed	50 / 264 (18.94%)	34 / 266 (12.78%)	18 / 88 (20.45%)
occurrences (all)	73	62	29
Asthenia			
subjects affected / exposed	49 / 264 (18.56%)	32 / 266 (12.03%)	7 / 88 (7.95%)
occurrences (all)	102	47	8
Oedema peripheral			
subjects affected / exposed	21 / 264 (7.95%)	26 / 266 (9.77%)	5 / 88 (5.68%)
occurrences (all)	34	32	6
Mucosal inflammation			
subjects affected / exposed	26 / 264 (9.85%)	8 / 266 (3.01%)	3 / 88 (3.41%)
occurrences (all)	29	9	6
Influenza like illness			
subjects affected / exposed	18 / 264 (6.82%)	11 / 266 (4.14%)	5 / 88 (5.68%)
occurrences (all)	22	23	7
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	88 / 264 (33.33%)	87 / 266 (32.71%)	33 / 88 (37.50%)
occurrences (all)	133	140	44
Diarrhoea			
subjects affected / exposed	68 / 264 (25.76%)	67 / 266 (25.19%)	14 / 88 (15.91%)
occurrences (all)	119	107	19
Constipation			
subjects affected / exposed	50 / 264 (18.94%)	44 / 266 (16.54%)	20 / 88 (22.73%)
occurrences (all)	73	51	27
Vomiting			
subjects affected / exposed	55 / 264 (20.83%)	38 / 266 (14.29%)	19 / 88 (21.59%)
occurrences (all)	79	53	24
Abdominal pain			
subjects affected / exposed	25 / 264 (9.47%)	36 / 266 (13.53%)	9 / 88 (10.23%)
occurrences (all)	33	53	14
Stomatitis			
subjects affected / exposed	28 / 264 (10.61%)	21 / 266 (7.89%)	8 / 88 (9.09%)
occurrences (all)	34	33	10
Abdominal pain upper			
subjects affected / exposed	22 / 264 (8.33%)	21 / 266 (7.89%)	1 / 88 (1.14%)
occurrences (all)	27	29	1
Dyspepsia			
subjects affected / exposed	16 / 264 (6.06%)	20 / 266 (7.52%)	7 / 88 (7.95%)
occurrences (all)	18	21	9
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	42 / 264 (15.91%)	33 / 266 (12.41%)	6 / 88 (6.82%)
occurrences (all)	54	50	6
Dyspnoea			
subjects affected / exposed	34 / 264 (12.88%)	29 / 266 (10.90%)	13 / 88 (14.77%)
occurrences (all)	42	43	16
Epistaxis			
subjects affected / exposed	18 / 264 (6.82%)	19 / 266 (7.14%)	2 / 88 (2.27%)
occurrences (all)	23	22	2
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	47 / 264 (17.80%)	39 / 266 (14.66%)	13 / 88 (14.77%)
occurrences (all)	51	46	13
Palmer-plantar erthrodysaesthesia syndrome			
subjects affected / exposed	33 / 264 (12.50%)	43 / 266 (16.17%)	1 / 88 (1.14%)
occurrences (all)	69	102	3
Rash			
subjects affected / exposed	18 / 264 (6.82%)	15 / 266 (5.64%)	6 / 88 (6.82%)
occurrences (all)	21	25	6
Pruritus			
subjects affected / exposed	13 / 264 (4.92%)	13 / 266 (4.89%)	7 / 88 (7.95%)
occurrences (all)	15	13	7
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 264 (5.68%)	15 / 266 (5.64%)	6 / 88 (6.82%)
occurrences (all)	16	16	7
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	32 / 264 (12.12%)	25 / 266 (9.40%)	7 / 88 (7.95%)
occurrences (all)	42	27	8
Arthralgia			
subjects affected / exposed	28 / 264 (10.61%)	23 / 266 (8.65%)	10 / 88 (11.36%)
occurrences (all)	35	30	17
Back pain			
subjects affected / exposed	23 / 264 (8.71%)	27 / 266 (10.15%)	7 / 88 (7.95%)
occurrences (all)	24	36	11
Myalgia			
subjects affected / exposed	18 / 264 (6.82%)	16 / 266 (6.02%)	4 / 88 (4.55%)
occurrences (all)	23	20	5
Muscle spasms			
subjects affected / exposed	17 / 264 (6.44%)	11 / 266 (4.14%)	7 / 88 (7.95%)
occurrences (all)	18	11	9
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	25 / 264 (9.47%)	26 / 266 (9.77%)	5 / 88 (5.68%)
occurrences (all)	39	32	8

Upper respiratory tract infection			
subjects affected / exposed	21 / 264 (7.95%)	23 / 266 (8.65%)	7 / 88 (7.95%)
occurrences (all)	34	24	7
Nasopharyngitis			
subjects affected / exposed	21 / 264 (7.95%)	19 / 266 (7.14%)	1 / 88 (1.14%)
occurrences (all)	27	27	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	38 / 264 (14.39%)	38 / 266 (14.29%)	9 / 88 (10.23%)
occurrences (all)	50	45	10
Hypokalaemia			
subjects affected / exposed	16 / 264 (6.06%)	21 / 266 (7.89%)	8 / 88 (9.09%)
occurrences (all)	28	36	19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2016	This global amendment increased the number of allowable prior lines of therapy from 2 to 3; modified efficacy evaluation timing; and clarified eligibility.
09 February 2017	In this global amendment the requirement for 3 prior anti-HER2 targeted therapies (trastuzumab, pertuzumab, and T-DM1) was liberalized. After this amendment, subjects were required to have at least 2 prior lines of anti-HER2 targeted therapies in the MBC setting before study entry, 1 of which must have been pertuzumab.
26 January 2018	An additional non-randomized cohort was added to demonstrate tolerability of lowering infusion duration from 120 minutes in Cycle 1 to 30 minutes in Cycle 2 and thereafter. To ensure that eligibility for randomized versus infusion sub-study populations were non-overlapping, eligibility for this cohort included at least 4 prior lines of therapy for metastatic disease. Randomized subjects received 1 to 3 lines of prior therapy, whereas infusion sub-study subjects received at least 4 prior lines.
08 June 2020	This global amendment limited study procedures that may increase risk of iatrogenic exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) while preserving the ability to collect necessary safety and efficacy data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36332179

http://www.ncbi.nlm.nih.gov/pubmed/33480963