Clinical trial results:
Pertuzumab + trastuzumab (PH) versus PH plus metronomic chemotherapy (PHM) in the elderly HER2+ metastatic breast cancer population who may continue on T-DM1 alone following disease progression while on PH / PHM: an open-label multicenter randomized phase II selection trial of the EORTC Elderly Task Force and Breast Cancer Group

Summary

EudraCT number	2011-006342-32
Trial protocol	BE IT PT NL GB SE
Global end of trial date	11 August 2022

Results information

Result version number	v1 (current)
This version publication date	20 August 2023
First version publication date	20 August 2023

Trial information

Trial identification

Sponsor protocol code	75111-10114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01597414
WHO universal trial number (UTN)	-
Other trial identifiers	NA: NA

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Regulatory Affairs Department, EORTC, 0032 27741074, regulatory@eortc.org
Scientific contact	Regulatory Affairs Department, EORTC, 0032 27741074, regulatory@eortc.org

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	26 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2017
Global end of trial reached?	Yes
Global end of trial date	11 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy (as measured by progression free survival at 6 months) of pertuzumab combined with trastuzumab (PH) or PH plus metronomic chemotherapy (PHM) in an elderly metastatic breast cancer population and to select attractive treatments for further development in phase III.

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Because of the under-representation of older patients in clinical trials, there is a lack of evidence-based clinical recommendations for older HER-2 positive breast cancer patients. Several different chemotherapy options in combination with trastuzumab are used, although there is a lack of data from randomized trials in this elderly population which is especially marked for non-fit individuals. Weekly paclitaxel, capecitabine and metronomic chemotherapy (low doses of oral cyclophosphamide and methotrexate) are chemotherapy options with proven efficacy and good safety profile in older patients, and trastuzumab is often added to these regimens. There is no real standard of care in this population , but chemotherapy regimens in combination with trastuzumab are often used.
Results of the phase 3 CLEOPATRA study, published in 2012, established docetaxel plus trastuzumab and pertuzumab as a new first-line standard of care for this population. However, docetaxel is a chemotherapeutic agent with well known and clinically relevant toxicity, affecting quality of life. It was also known that metronomic chemotherapy with oral cyclophosphamide is an active chemotherapy regimen with minor toxicity and is thus suitable for older patients. There were, however, no relevant data for the effects of metronomic cyclophosphamide combined with anti-HER2 therapy in patients with HER2-positive metastatic breast cancer. The present study aimed to investigate whether anti-HER2 blockade alone could be adequately effective in this
population or whether addition of a milder type of chemotherapy is required.

Evidence for comparator: -

Actual start date of recruitment	02 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 6

Country: Number of subjects enrolled	Belgium: 50
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	80
EEA total number of subjects	74

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)	2
From 65 to 84 years	69
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Between July 2, 2013, and May 10, 2016, 80 patients were enrolled by 19 institutions in 7 countries. After review, 3 patients were found not eligible to this trial (two due to previous medical history including secondary cancers, one patient younger than 70 years old not fulfilling eligibility criteria based on ADL or IADL or CCI criteria).

Pre-assignment

Screening details:

- HER-2 positive invasive breast cancer
- Newly diagnosed or recurrent stage IV disease
- Measurable (RECIST v. 1.1) or evaluable disease
- Age ≥ 70 years of age, or ≥ 60 years old with required number of dependencies (defined based on ADL or iADL or CCI evaluations)

Period 1

Period 1 title	Randomization (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 + pertuzumab

Arm description:

Treatment cycles are defined as a 3 week period. Both treatments were given until disease progression or unacceptable toxicity or patient's refusal.
Dose reductions were not allowed. In case of treatment delay of 3 weeks or more, the patient would discontinue the protocol-specified treatment.
Tumour evaluation was done every 9 weeks, independently of treatment delays. After disease progression, all patients could be treated as per standard practice at the physician’s discretion, but they were also given the option of receiving intravenous trastuzumab-DM1 as part of the protocol treatment. Those patients are reported as having completed Period 1 as per EUDRACT reporting system requirements, although they all discontinued randomized treatment due to progressive disease.
Cardiac monitoring was done with regular evaluation of LVEF every 9 weeks. For patients with progressive disease limited to the brain, a protocol amendment implemented in July 4, 2014 allowed continuation on the prot

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Trastuzumab should be administered at loading dose of 8 mg/kg of body weight on cycle 1, followed by a maintenance dose of 6 mg/kg every 3 weeks. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by more than ± 10% from baseline. The initial dose of trastuzumab should be administered over 90 (± 10) minutes and patients observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever, chills etc. If the infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes and patients should be observed for a further 30 minutes. If a patient misses a dose of trastuzumab by more than 1 week, a re-loading dose of trastuzumab (8 mg/kg) may be given in the same fashion as for cycle 1. If the patient misses a maintenance dose of treatment by one week or less, then the usual maintenance dose should be given as soon as possible.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Pertuzumab should be given at a fixed loading dose of 840 mg on cycle 1, followed by 420 mg for subsequent cycles, every 3 weeks. The initial dose of pertuzumab should be given after the infusion of trastuzumab (following the observation period) and administered over 60 (± 10) minutes with patients to be observed for a further 60 minutes. If a patient misses a dose of pertuzumab by less than 3 weeks (i.e. the time between two sequential pertuzumab infusions is less than 6 weeks), no re-loading dose is required, but the maintenance dose of 420 mg pertuzumab should be administered as soon as possible.

Arm title	Trastuzumab + pertuzumab + metronomic cyclophosphamide

Arm description:

Treatment cycles are defined as a 3 week period. Both treatments were given until disease progression or unacceptable toxicity or patient's refusal. Tumour evaluation was done every 9 weeks, independently of treatment delays. After disease progression, all patients could be treated as per standard practice at the physician’s discretion, but they were also given the option of receiving intravenous trastuzumab-DM1 as part of the protocol treatment.Those patients are reported as having completed Period 1 as per EUDRACT reporting system requirements, although they all discontinued randomized treatment due to progressive disease.
Cardiac monitoring was done with regular evaluation of LVEF every 9 weeks. For patients with progressive disease limited to the brain, a protocol amendment implemented in July 4, 2014 allowed continuation on the protocol treatment after local brain therapy.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Trastuzumab should be administered at loading dose of 8 mg/kg of body weight on cycle 1, followed by a maintenance dose of 6 mg/kg every 3 weeks. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by more than ± 10% from baseline. The initial dose of trastuzumab should be administered over 90 (± 10) minutes and patients observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever, chills etc. If the infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes and patients should be observed for a further 30 minutes. If a patient misses a dose of trastuzumab by more than 1 week, a re-loading dose of trastuzumab (8 mg/kg) may be given in the same fashion as for cycle 1. If the patient misses a maintenance dose of treatment by one week or less, then the usual maintenance dose should be given as soon as possible.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Pertuzumab should be given at a fixed loading dose of 840 mg on cycle 1, followed by 420 mg for subsequent cycles, every 3 weeks. The initial dose of pertuzumab should be given after the infusion of trastuzumab (following the observation period) and administered over 60 (± 10) minutes with patients to be observed for a further 60 minutes. If a patient misses a dose of pertuzumab by less than 3 weeks (i.e. the time between two sequential pertuzumab infusions is less than 6 weeks), no re-loading dose is required, but the maintenance dose of 420 mg pertuzumab should be administered as soon as possible.

Investigational medicinal product name	Metronomic cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide should be taken orally by the patient, at a daily dose of 50 mg/day, approximately at the same hour every day. If any intake should be missed/ forgotten by the patient, the normal schedule and dosage should be maintained, without trying to catch up with the dose that has been skipped.
In case that a patient only progresses in the brain, and the PHM treatment continues, a treatment delay

of more than 21 days can be accepted in order for him/her to complete brain metastatic treatment (whole brain irradiation, radiosurgery or equivalent). However, treatment should be resumed at the latest three weeks after the day of completion of local treatment for brain disease. No premedication/ supportive treatment is needed for metronomic chemotherapy. No vital signs assessment required for cyclophosphamide.

Number of subjects in period 1	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab + metronomic cyclophosphamide
Started	39	41
Completed	18	22
Not completed	21	19
Adverse event, non-fatal	3	7
Toxicity not related to treatment	1	-
Death not due to malignant disease or toxicity	3	-
Unknown	-	1
Other malignancy	1	2
Patient no longer able to come	-	1
Still on treatment at time of analysis	1	-
Progressive disease, no switch to T-DM1	7	2
Patient's decision (not related to toxicity)	5	4
Lost to follow-up	-	1
Heart failure	-	1

Period 2

Period 2 title	Post-progression (optional)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Trastuzumab-DM1

Arm description:

Treatment cycles are defined as a 3 week period.
T-DM1 treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal.

Arm type	Experimental

Investigational medicinal product name	Trastuzumab-DM1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

T-DM1 consists of the trastuzumab antibody conjugated to DM1. After binding to HER-2, T-DM1 is internalized and DM1 induces cancer cell death by inhibiting assembly of microtubules. T-DM1 should be given at a dose of 3.6 mg/kg IV every 3 weeks. The total dose depends on the patient's weight on day 1 of each cycle.

Number of subjects in period 2	Trastuzumab-DM1
Started	40
Completed	0
Not completed	40
Physician decision	1
Bad general status	1
Adverse event, non-fatal	2
Death not due to malignant disease or toxicity	1
Cognitive decline	2
Still on treatment at time of analysis	1
Patient's decision (not related to toxicity)	3
Progressive disease	28
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab + pertuzumab

Reporting group description:

Treatment cycles are defined as a 3 week period. Both treatments were given until disease progression or unacceptable toxicity or patient's refusal.
Dose reductions were not allowed. In case of treatment delay of 3 weeks or more, the patient would discontinue the protocol-specified treatment.
Tumour evaluation was done every 9 weeks, independently of treatment delays. After disease progression, all patients could be treated as per standard practice at the physician’s discretion, but they were also given the option of receiving intravenous trastuzumab-DM1 as part of the protocol treatment. Those patients are reported as having completed Period 1 as per EUDRACT reporting system requirements, although they all discontinued randomized treatment due to progressive disease.
Cardiac monitoring was done with regular evaluation of LVEF every 9 weeks. For patients with progressive disease limited to the brain, a protocol amendment implemented in July 4, 2014 allowed continuation on the prot

Reporting group title	Trastuzumab + pertuzumab + metronomic cyclophosphamide

Reporting group description:

Treatment cycles are defined as a 3 week period. Both treatments were given until disease progression or unacceptable toxicity or patient's refusal. Tumour evaluation was done every 9 weeks, independently of treatment delays. After disease progression, all patients could be treated as per standard practice at the physician’s discretion, but they were also given the option of receiving intravenous trastuzumab-DM1 as part of the protocol treatment.Those patients are reported as having completed Period 1 as per EUDRACT reporting system requirements, although they all discontinued randomized treatment due to progressive disease.
Cardiac monitoring was done with regular evaluation of LVEF every 9 weeks. For patients with progressive disease limited to the brain, a protocol amendment implemented in July 4, 2014 allowed continuation on the protocol treatment after local brain therapy.

Reporting group values	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab + metronomic cyclophosphamide	Total
Number of subjects	39	41	80
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)	2	0	2
From 65-84 years	33	36	69
85 years and over	4	5	9
Age continuous Units: years			
median	76.2	77.3	
full range (min-max)	61.4 to 91.4	67.7 to 89.6	-
Gender categorical Units: Subjects			
Female	39	41	80
Male	0	0	0

WHO performance status			
PS = Performance status			
Units: Subjects			
PS = 0	10	17	27
PS = 1	17	17	34
PS = 2	8	7	15
PS = 3	4	0	4
Hormone receptor status			
ER = Estrogen receptor PgR = Progesterone receptor			
Units: Subjects			
ER- and PgR-	12	13	25
ER+ and/or PgR+	27	28	55
Previous (neo)adjuvant chemotherapy* or anti-HER2 therapy			
* Previous (neo)adjuvant chemotherapy with or without anti-HER2 therapy			
Units: Subjects			
No previous line	29	36	65
>= 1 lines	10	5	15
Previous anti-HER2 therapy for metastatic breast cancer Units: Subjects			
No	36	37	73
Yes	3	4	7
Previous adjuvant endocrine therapy Units: Subjects			
No	24	31	55
Yes	15	9	24
Missing	0	1	1
Previous endocrine therapy for metastatic breast cancer Units: Subjects			
No	33	35	68
Yes	5	5	10
Missing	1	1	2
Previous breast surgery Units: Subjects			
No	17	22	39
Palliative intent	1	2	3
Curative intent	21	17	38
Visceral involvement Units: Subjects			
No	1	4	5
Yes	38	36	74
Missing	0	1	1
G8 score at baseline Units: Subjects			
<=14	27	28	55
>14 (normal)	12	12	24
Missing	0	1	1
CCI score at baseline			
CCI = Charlson Comorbidity Index			

Units: Subjects			
CCI = 0 (normal)	20	27	47
CCI = 1 or 2	15	10	25
CCI > 2	4	3	7
Missing	0	1	1
ADL score at baseline			
ADL = Activities of Daily Living			
Units: Subjects			
ADL <= 3	4	2	6
ADL = 4 or 5	9	10	19
ADL = 6 (normal)	26	28	54
Missing	0	1	1
IADL score at baseline			
IADL = Instrumental Activities of Daily Living			
Units: Subjects			
IADL <= 3	6	7	13
IADL = 4 or 5	7	5	12
IADL = 6 to 8 (normal)	26	28	54
Missing	0	1	1
SPPB score at baseline			
SPPB = Short Physical Performance Battery			
Units: Subjects			
SPPB <= 7	20	17	37
7 < SPPB <= 9	9	11	20
9 < SPPB <= 12	5	8	13
Missing	5	5	10
Social situation Units: Subjects			
At home by myself	14	19	33
At home with someone	19	19	38
Institutional care	4	1	5
Missing	2	2	4
GDS-4 score at baseline			
GDS-4 = Geriatric Depression Scale 4 items			
Units: Subjects			
GDS-4 = 0 (normal)	9	16	25
GDS-4 = 1	12	14	26
GDS-4 = 2	7	7	14
GDS-4 = 3-4	11	2	13
Missing	0	2	2

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients were analyzed in the arm they were allocated by randomization

Subject analysis set title	T-DM1 population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who started on T-DM1 treatment, which was offered after disease progression on

randomized treatment, either trastuzumab + pertuzumab or trastuzumab + pertuzumab + metronomic cyclophosphamide

Subject analysis set title	Per protocol population with measurable disease
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who are eligible and have started their allocated treatment and had measurable disease at baseline.

Subject analysis set title	T-DM1 population with measurable disease
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who started T-DM1 treatment with measurable disease

Reporting group values	ITT	T-DM1 population	Per protocol population with measurable disease
Number of subjects	80	40	72
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)	2	2	1
From 65-84 years	69	33	62
85 years and over	9	5	9
Age continuous Units: years			
median	76.7	74.4	77.2
full range (min-max)	61.4 to 91.4	61.4 to 89.4	61.4 to 91.4
Gender categorical Units: Subjects			
Female	80	40	72
Male	0	0	0
WHO performance status			
PS = Performance status			
Units: Subjects			
PS = 0	27	12	23
PS = 1	34	17	31
PS = 2	15	10	14
PS = 3	4	1	4
Hormone receptor status			
ER = Estrogen receptor PgR = Progesterone receptor			
Units: Subjects			
ER- and PgR-	25	13	24
ER+ and/or PgR+	55	27	48
Previous (neo)adjuvant chemotherapy* or anti-HER2 therapy			
* Previous (neo)adjuvant chemotherapy with or without anti-HER2 therapy			
Units: Subjects			

No previous line	65	33	59
>= 1 lines	15	7	13
Previous anti-HER2 therapy for metastatic breast cancer Units: Subjects			
No	73	37	66
Yes	7	7	6
Previous adjuvant endocrine therapy Units: Subjects			
No	55	27	50
Yes	24	13	21
Missing	1	0	1
Previous endocrine therapy for metastatic breast cancer Units: Subjects			
No	68	35	62
Yes	10	5	8
Missing	2	0	2
Previous breast surgery Units: Subjects			
No	39	20	37
Palliative intent	3	2	2
Curative intent	38	18	33
Visceral involvement Units: Subjects			
No	5	1	4
Yes	74	39	68
Missing	1	0	0
G8 score at baseline Units: Subjects			
<=14	55	23	49
>14 (normal)	24	16	22
Missing	1	1	1
CCI score at baseline			
CCI = Charlson Comorbidity Index			
Units: Subjects			
CCI = 0 (normal)	47	27	42
CCI = 1 or 2	25	9	23
CCI > 2	7	3	6
Missing	1	1	1
ADL score at baseline			
ADL = Activities of Daily Living			
Units: Subjects			
ADL <= 3	6	4	5
ADL = 4 or 5	19	10	18
ADL = 6 (normal)	54	25	48
Missing	1	1	1
IADL score at baseline			
IADL = Instrumental Activities of Daily Living			
Units: Subjects			
IADL <= 3	13	6	12
IADL = 4 or 5	12	8	10

IADL = 6 to 8 (normal)	54	25	49
Missing	1	1	1
SPPB score at baseline			
SPPB = Short Physical Performance Battery			
Units: Subjects			
SPPB <= 7	37	16	35
7 < SPPB <= 9	20	10	15
9 < SPPB <= 12	13	8	13
Missing	10	6	9
Social situation			
Units: Subjects			
At home by myself	33	13	31
At home with someone	38	22	33
Institutional care	5	3	4
Missing	4	2	4
GDS-4 score at baseline			
GDS-4 = Geriatric Depression Scale 4 items			
Units: Subjects			
GDS-4 = 0 (normal)	25	13	23
GDS-4 = 1	26	13	24
GDS-4 = 2	14	5	13
GDS-4 = 3-4	13	8	10
Missing	2	1	2

Reporting group values	T-DM1 population with measurable disease		
Number of subjects	36		
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)	1		
From 65-84 years	30		
85 years and over	5		
Age continuous			
Units: years			
median	74.4		
full range (min-max)	61.4 to 89.6		
Gender categorical			
Units: Subjects			
Female	36		
Male	0		
WHO performance status			
PS = Performance status			
Units: Subjects			
PS = 0	11		

PS = 1	5		
PS = 2	9		
PS = 3	1		
Hormone receptor status			
ER = Estrogen receptor PgR = Progesterone receptor			
Units: Subjects			
ER- and PgR-	13		
ER+ and/or PgR+	23		
Previous (neo)adjuvant chemotherapy* or anti-HER2 therapy			
* Previous (neo)adjuvant chemotherapy with or without anti-HER2 therapy			
Units: Subjects			
No previous line	30		
>= 1 lines	6		
Previous anti-HER2 therapy for metastatic breast cancer Units: Subjects			
No	33		
Yes	3		
Previous adjuvant endocrine therapy Units: Subjects			
No	25		
Yes	11		
Missing	0		
Previous endocrine therapy for metastatic breast cancer Units: Subjects			
No	32		
Yes	4		
Missing	0		
Previous breast surgery Units: Subjects			
No	19		
Palliative intent	1		
Curative intent	16		
Visceral involvement Units: Subjects			
No	1		
Yes	35		
Missing	0		
G8 score at baseline Units: Subjects			
<=14	20		
>14 (normal)	15		
Missing	1		
CCI score at baseline			
CCI = Charlson Comorbidity Index			
Units: Subjects			
CCI = 0 (normal)	24		
CCI = 1 or 2	8		
CCI > 2	3		

Missing	1		
ADL score at baseline			
ADL = Activities of Daily Living			
Units: Subjects			
ADL <= 3	3		
ADL = 4 or 5	10		
ADL = 6 (normal)	22		
Missing	1		
IADL score at baseline			
IADL = Instrumental Activities of Daily Living			
Units: Subjects			
IADL <= 3	5		
IADL = 4 or 5	7		
IADL = 6 to 8 (normal)	23		
Missing	1		
SPPB score at baseline			
SPPB = Short Physical Performance Battery			
Units: Subjects			
SPPB <= 7	15		
7 < SPPB <= 9	8		
9 < SPPB <= 12	8		
Missing	5		
Social situation Units: Subjects			
At home by myself	13		
At home with someone	19		
Institutional care	2		
Missing	2		
GDS-4 score at baseline			
GDS-4 = Geriatric Depression Scale 4 items			
Units: Subjects			
GDS-4 = 0 (normal)	12		
GDS-4 = 1	13		
GDS-4 = 2	5		
GDS-4 = 3-4	5		
Missing	1		

End points

End points reporting groups

Reporting group title	Trastuzumab + pertuzumab

Reporting group description:

Treatment cycles are defined as a 3 week period. Both treatments were given until disease progression or unacceptable toxicity or patient's refusal.
Dose reductions were not allowed. In case of treatment delay of 3 weeks or more, the patient would discontinue the protocol-specified treatment.
Tumour evaluation was done every 9 weeks, independently of treatment delays. After disease progression, all patients could be treated as per standard practice at the physician’s discretion, but they were also given the option of receiving intravenous trastuzumab-DM1 as part of the protocol treatment. Those patients are reported as having completed Period 1 as per EUDRACT reporting system requirements, although they all discontinued randomized treatment due to progressive disease.
Cardiac monitoring was done with regular evaluation of LVEF every 9 weeks. For patients with progressive disease limited to the brain, a protocol amendment implemented in July 4, 2014 allowed continuation on the prot

Reporting group title	Trastuzumab + pertuzumab + metronomic cyclophosphamide

Reporting group description:

Treatment cycles are defined as a 3 week period. Both treatments were given until disease progression or unacceptable toxicity or patient's refusal. Tumour evaluation was done every 9 weeks, independently of treatment delays. After disease progression, all patients could be treated as per standard practice at the physician’s discretion, but they were also given the option of receiving intravenous trastuzumab-DM1 as part of the protocol treatment.Those patients are reported as having completed Period 1 as per EUDRACT reporting system requirements, although they all discontinued randomized treatment due to progressive disease.
Cardiac monitoring was done with regular evaluation of LVEF every 9 weeks. For patients with progressive disease limited to the brain, a protocol amendment implemented in July 4, 2014 allowed continuation on the protocol treatment after local brain therapy.

Reporting group title	Trastuzumab-DM1

Reporting group description:

Treatment cycles are defined as a 3 week period.
T-DM1 treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients were analyzed in the arm they were allocated by randomization

Subject analysis set title	T-DM1 population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who started on T-DM1 treatment, which was offered after disease progression on randomized treatment, either trastuzumab + pertuzumab or trastuzumab + pertuzumab + metronomic cyclophosphamide

Subject analysis set title	Per protocol population with measurable disease
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who are eligible and have started their allocated treatment and had measurable disease at baseline.

Subject analysis set title	T-DM1 population with measurable disease
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who started T-DM1 treatment with measurable disease

Primary: Progression-Free Survival (PFS) rate at 6 months

End point title	Progression-Free Survival (PFS) rate at 6 months

End point description:

Progression free survival is defined as the time between the date of randomization and the date of disease progression or death. If neither event has been observed, then the patient is censored on the date of the last follow up examination.
Progression of the disease is defined based on one or several of the following criteria:
Documented radiological progression as defined by RECIST 1.1.
Development of new lesions
Unequivocal (according to physician's assessment) deterioration of non-measurable lesions.
PFS (including the primary estimate at 6 months) is summarized by the empirical distribution function for interval censored data.

One patient in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group was excluded from the interval-censored analysis because she had received trastuzumab and pertuzumab treatment during the first day but immediately stopped because of toxicity and withdrew consent.

End point type	Primary

End point timeframe:

6 months from randomisation

End point values	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab + metronomic cyclophosphamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: % at 6 months				
number (confidence interval 95%)	46.2 (30.2 to 60.7)	73.4 (56.6 to 84.6)		

Statistical analyses

Statistical analysis title	Primary analysis (Sargent and Goldberg design)

Statistical analysis description:

Both treatment groups were compared for PFS at 6 months with the aim of assessing whether one of the groups seemed superior and promising for further development. Assuming that PFS at 6 months for one group is 55%, and for the other group 40%, a sample size of 40 patients per group would result in an estimated probability of selecting the better treatment group of 0·81. With this design, there was a 63·5% chance of observing at least a 10% difference favouring the best regimen.

Comparison groups	Trastuzumab + pertuzumab v Trastuzumab + pertuzumab + metronomic cyclophosphamide
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Risk difference (RD)
Point estimate	27.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	49.4

Notes:

[1] - The decision rule for the primary analysis is based on the observed difference in PFS rate at 6 months between the two treatment arms. Corresponding confidence interval is providing as per EUDRACT reporting system requirements but is not used for the decision rule.
Results of primary analysis are reported when data maturity for primary endpoint has been reached after all patients have been followed up for 6 months (database lock 19 April 2017 ,median follow-up of 20.7 months)

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is measured from the date of randomization to the date of death whatever the cause of death. Patients who are alive are censored at the last date known to be alive. OS is estimated by the Kaplan-Meier (KM) method. Median OS is provided with its 95% confidence interval (note that if upper boundary of the 95% confidence interval could not be estimated, it is entered as 100% to allow data entry into the EUDRACT reporting system).
OS results are reported at the time of final analysis with a data cut off dated 26 March 2021 corresponding to a median follow-up of 54.0 months.

End point type	Secondary

End point timeframe:

From randomisation until end of follow-up

End point values	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab + metronomic cyclophosphamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41[2]		
Units: Months				
median (confidence interval 95%)	32.1 (16.6 to 44.7)	37.5 (23.2 to 100)		

Notes:

[2] - Upper boundary of 95%CI not estimable, assigned to 100 based on EUDRACT reporting requirements

Statistical analyses

No statistical analyses for this end point

Secondary: Breast cancer specific survival (BCSS)

End point title	Breast cancer specific survival (BCSS)

End point description:

Breast cancer specific survival is measured from the date of randomization to the date of death due to breast cancer. Deaths due to non-breast cancer causes are analyzed as competing risks. Patients who are alive are censored at the last date known to be alive. BCSS is estimated by the cumulative incidence function method. Median BCSS is provided with its 95% confidence interval (note that if upper boundary of the 95% confidence interval could not be estimated, it is entered as 100% to allow data entry into the EUDRACT reporting system).
BCSS results are reported at the time of final analysis with a data cut off dated 26 March 2021 corresponding to a median follow-up of 54.0 months.

End point type	Secondary

End point timeframe:

From randomisation until end of follow-up

End point values	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab + metronomic cyclophosphamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[3]	41[4]		
Units: Months				
median (confidence interval 95%)	44.7 (32.3 to 100)	46.8 (28.7 to 100)		

Notes:

[3] - Upper boundary of 95%CI not estimable, assigned to 100 based on EUDRACT reporting requirements

[4] - Upper boundary of 95%CI not estimable, assigned to 100 based on EUDRACT reporting requirements

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor response

End point title	Tumor response

End point description:

Responses were calculated according to RECIST version 1.1 on the corresponding per-protocol population (defined as all eligible patients who started their allocated treatment) with measurable disease at baseline. Tumour evaluation was done every 9 weeks, independently of treatment delays
Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.
Early death is defined as any death occurring before the first per protocol time point of tumor reevaluation.
Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

End point type	Secondary

End point timeframe:

from the start of study treatment until the end of treatment

End point values	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab + metronomic cyclophosphamide	Per protocol population with measurable disease	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	36	72	
Units: Subjects				
Complete response	1	1	2	
Partial response	15	18	33	
Stable disease	12	12	24	
Progressive disease	4	4	8	
Early death	2	0	2	
Not evaluable	2	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS rate at 6 months after T-DM1 start

End point title	PFS rate at 6 months after T-DM1 start

End point description:

Progression free survival after T-DM1 is defined similarly to PFS, with the following differences:
This analysis is restricted to patients who received T-DM1
A new baseline is taken prior to start of T-DM1 to evaluate progression on T-DM1.
The endpoint is measured from the start of T-DM1 administration.
PFS after T-DM1 start is summarized by the empirical distribution function for interval censored data.
PFS after T-DM1 start is reported at the time of final analysis with a data cut off dated 26 March 2021 corresponding to a median follow-up on T-DM1 of 33.7 months.

End point type	Secondary

End point timeframe:

from start of T-DM1 until 6 months after start of T-DM1

End point values	Trastuzumab-DM1			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: % at 6 months after T-DM1 start				
number (confidence interval 95%)	43.6 (27.7 to 58.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor response on T-DM1

End point title	Tumor response on T-DM1

End point description:

Responses were calculated according to RECIST version 1.1 on the corresponding T-DM1 population with measurable disease.
Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.
Early death is defined as any death occurring before the first time point of tumor reevaluation.
Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

End point type	Secondary

End point timeframe:

From the last measurement of lesions prior to administration of T-DM1 as a new baseline until end of T-DM1 treatment

End point values	Trastuzumab-DM1			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Subjects				
Complete response	0			
Partial response	9			
Stable disease	17			
Progressive disease	4			
Early death	3			
Not evaluable	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs are reported from the first administration of randomized treatment until the last administration of randomized treatment or start of T-DM1 whichever occurred last.
SAEs are reported until the end of follow-up period.

Adverse event reporting additional description:

AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Trastuzumab + Pertuzumab + metronomic cyclophosphamide
Reporting group description: -	
Reporting group title	Trastuzumab + Pertuzumab

Reporting group description: -

Serious adverse events	Trastuzumab + Pertuzumab + metronomic cyclophosphamide	Trastuzumab + Pertuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 41 (56.10%)	23 / 39 (58.97%)	
number of deaths (all causes)	22	27	
number of deaths resulting from adverse events	2	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MYELODYSPLASTIC SYNDROME			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYELOPROLIFERATIVE NEOPLASM			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ARTERIAL THROMBOSIS			

alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ISCHAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
SUDDEN DEATH	Additional description: Fatal adverse event, occurred during period 1		
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ASTHENIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
HYPERSENSITIVITY			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAPHYLACTIC REACTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	4 / 41 (9.76%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOSPASM			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE	Additional description: Fatal adverse event, occurred during period 1		
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
ANXIETY			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELIRIUM			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HALLUCINATION, VISUAL			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
TACHYCARDIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT VENTRICULAR DYSFUNCTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY STENOSIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE	Additional description: The case of fatal adverse event, occurred during period 1		
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
CARDIAC ARREST	Additional description: Fatal adverse event, occurred during period 1		
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ATRIAL FIBRILLATION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
COGNITIVE DISORDER			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
SPLENIC HAEMORRHAGE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
MENIERE'S DISEASE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANURIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE	Additional description: Fatal adverse event, occurred during period 2, i.e. after start of T-DM1 treatment		
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN PAIN			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
SKIN INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA	Additional description: Fatal adverse event, occurred during period 2, i.e. after start of T-DM1 treatment		
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
PERITONITIS	Additional description: Fatal adverse event, occurred during period 1		
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
INTERVERTEBRAL DISCITIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL BACTERAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPOGLYCAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CACHEXIA	Additional description: Fatal adverse event, occurred during period 2, i.e. after start of T-DM1 treatment		
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Trastuzumab + Pertuzumab + metronomic cyclophosphamide	Trastuzumab + Pertuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	38 / 39 (97.44%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MYELODYSPLASTIC SYNDROME			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ULCERATING CHARACTER OF BREASTCARCINOMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
HYPOTENSIVE SYMPTOMS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ARTERIAL THROMBOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HEMATOMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	4	
HOT FLASHES			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	4	
HYPERTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	9 / 41 (21.95%)	9 / 39 (23.08%)	
occurrences (all)	20	22	
HYPOTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
LYMPHEDEMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences (all)	5	2	
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 41 (9.76%)	1 / 39 (2.56%)	
occurrences (all)	5	1	
PERIPHERAL ISCHEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
Surgical and medical procedures			
PORT-A-CATH PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
WORSENING OF LEFT ARM FUNCTIONAL IMPOTENCE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CHILLS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	2 / 41 (4.88%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
COLD			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
COLDNESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
EDEMA LIMBS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 41 (17.07%)	6 / 39 (15.38%)	
occurrences (all)	16	6	
FACIAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	6	0	
FATIGUE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	33 / 41 (80.49%)	25 / 39 (64.10%)	
occurrences (all)	67	70	
FEVER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 41 (19.51%)	7 / 39 (17.95%)	
occurrences (all)	12	7	
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 41 (9.76%)	0 / 39 (0.00%)	
occurrences (all)	5	0	
HEAD INJURY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

INFUSION RELATED REACTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 41 (12.20%)	3 / 39 (7.69%)	
occurrences (all)	5	3	
IRRITABILITY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
LOCALIZED EDEMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
MALAISE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	3 / 39 (7.69%)	
occurrences (all)	2	4	
NIGHT SWEATING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
ODYNOPHAGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	14 / 41 (34.15%)	10 / 39 (25.64%)	
occurrences (all)	19	16	
PROBLEM WITH PORT-A-CATH			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
SUDDEN DEATH NOS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 41 (17.07%)	2 / 39 (5.13%)	
occurrences (all)	7	2	
Reproductive system and breast disorders			
BREAST PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
INTERMITTENT FLOW AT THE LEFT BREAST			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
LACTATION DISORDER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
MICTALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PELVIC PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
VAGINAL DRYNESS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
VULVAR AND GROIN PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
VULVAR MUCOSITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
BRONCHITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ALLERGIC RHINITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	3 / 39 (7.69%)	
occurrences (all)	2	3	
ASPIRATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ASTHMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
BRONCHIAL OBSTRUCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
BRONCHIAL STRICTURE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
BRONCHOSPASM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
CHYLOTHORAX			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
COMMON COLD			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	5	0	
COUGH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	13 / 41 (31.71%)	6 / 39 (15.38%)	
occurrences (all)	16	10	
DYSPNEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	12 / 41 (29.27%)	9 / 39 (23.08%)	
occurrences (all)	21	11	
EPISTAXIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 41 (12.20%)	8 / 39 (20.51%)	
occurrences (all)	6	13	
PNEUMOPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
LUNG INFILTRATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

NASAL DRYNESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
NOSE MUCOSITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PLEURAL EFFUSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
PNEUMONIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
PNEUMONITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
HOARSENESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PULMONARY CONSOLIDATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
RHINORRHEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences (all)	5	2	
SINUS DISORDER			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SORE THROAT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
THORACIC PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
VOICE ALTERATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
RESPIRATORY FAILURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
ANXIETY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 41 (9.76%)	3 / 39 (7.69%)	
occurrences (all)	5	3	
CONFUSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
DEPRESSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
HALLUCINATIONS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
INSOMNIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	4 / 39 (10.26%)	
occurrences (all)	2	5	
STRESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Investigations			
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ELEVATED UREUM LEVEL			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
GGT INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
INCREASED CRP			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
INCREASED LDH			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
WEIGHT LOSS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 41 (19.51%)	3 / 39 (7.69%)	
occurrences (all)	16	5	
Injury, poisoning and procedural complications			
DERMATITIS RADIATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
BRUISING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
FALL			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
HIP FRACTURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
TOE WOUNDS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
FRACTURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ATRIAL FIBRILLATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 41 (9.76%)	1 / 39 (2.56%)	
occurrences (all)	6	1	
CARDIAC ARREST			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CHEST PAIN - CARDIAC			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
EXTRASYSTOLES			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HEART FAILURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
LEFT VENTRICULAR SYSTOLIC DYSFUNCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
MITRAL VALVE DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PALPITATIONS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	

SINUS BRADYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SINUS TACHYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SYSTOLIC HEART MURMUR			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
TACHYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
VENTRICULAR EXTRASYSTOLES			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
ANXIETY FOR ALLERGIC REACTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
COGNITIVE DISTURBANCE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	3	2	
DIZZINESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 41 (14.63%)	2 / 39 (5.13%)	
occurrences (all)	7	2	
DYSGEUSIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	4 / 41 (9.76%)	1 / 39 (2.56%)	
occurrences (all)	5	1	
EXTRAPYRAMIDAL DISORDER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HEADACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 41 (14.63%)	4 / 39 (10.26%)	
occurrences (all)	7	5	
HYPOESTHESIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
LETHARGY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
MEMORY IMPAIRMENT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
MIGRAINE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	4	0	
NEURALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
NEUROLOGICAL DEGRADATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	

PARESE RIGHT LEG			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PARESTHESIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 41 (17.07%)	3 / 39 (7.69%)	
occurrences (all)	20	4	
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	6	2	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 41 (12.20%)	1 / 39 (2.56%)	
occurrences (all)	8	1	
POLYNEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SYNCOPE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
TETANY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
TREMOR			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
EPILEPTIC CRISIS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
LYMPH NODE PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
POSSIBLE MYELOPDYSPLASIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
TINNITUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
BALANCE DISORDER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
HEARING IMPAIRED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
MENIERE'S DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
VERTIGO			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
Eye disorders			
CHALAZION			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CONJUNCTIVITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 41 (14.63%)	0 / 39 (0.00%)	
occurrences (all)	7	0	
DRY EYE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
EYE DISTURBANCES, FLASHING AND ZIGZAG EFFECT (MIGRAINE)			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
EYE MUCOSITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
EYE PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
WATERING EYES			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
BLURRED VISION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	10 / 41 (24.39%)	8 / 39 (20.51%)	
occurrences (all)	14	11	
ABDOMINAL DISTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 41 (12.20%)	5 / 39 (12.82%)	
occurrences (all)	5	8	
ANAL HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
BLOATING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	3	
CONSTIPATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	13 / 41 (31.71%)	6 / 39 (15.38%)	
occurrences (all)	15	8	
DENTAL ABSCESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
DIARRHEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	29 / 41 (70.73%)	23 / 39 (58.97%)	
occurrences (all)	103	70	
DRY MOUTH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	

DYSPEPSIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
DYSPHAGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
ENTERITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
GASTRITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
GASTROENTERITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
GINGIVAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MOUTH ULCERS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
NAUSEA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	20 / 41 (48.78%)	10 / 39 (25.64%)	
occurrences (all)	30	14	
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
STOMATITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
TOOTHACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
VOMITING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 41 (17.07%)	5 / 39 (12.82%)	
occurrences (all)	10	6	
ORAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
ALOPECIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
BREAST SKIN REDNESS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
BRITTLE NAILS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
BROKEN NAILS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CELLULITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CRUSTED LESION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
CRUSTY LESION IN THE SCALP			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
CUTANEOUS RASH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
DECUBITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
DERMATITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	

DRY NAILS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
DRY SKIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	6 / 39 (15.38%)	
occurrences (all)	4	8	
ECZEMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
ERYTHEMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
ERYTHEMA MULTIFORME			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	3 / 39 (7.69%)	
occurrences (all)	4	3	
FISSURES			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
FOLLICULITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
GRANULOMA PYOGENICUM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HAND FISSURS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
ITCHING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
NAIL DISCOLORATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
NAIL PROBLEM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
NAIL RIDGING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
NASAL CRUST			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
PRURITUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 41 (14.63%)	4 / 39 (10.26%)	
occurrences (all)	9	10	
RASH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences (all)	3	0	

RASH ACNEIFORM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences (all)	5	2	
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
SEBORRHEIC DERMATITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
SKIN AND SUBCUTANEOUS DISORDER, OTHER SPECIFY : ONOCHOPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SKIN AND SUBCUTANEOUS TISSUE OTHER : XEROSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SKIN HYPERPIGMENTATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SKIN INDURATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
SKIN ULCERATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
STASE DERMATITIS			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
WEAK NAILS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
XERODERMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
NAIL CHANGES			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Renal and urinary disorders			
CHRONIC KIDNEY DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
ACUTE KIDNEY INJURY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	3	
CYSTITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
DYSURIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
POLYAKURIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
UNCOMFORTABLE ON PASSING URINE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
URINARY FREQUENCY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
URINARY INCONTINENCE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
URINARY TRACT PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	3 / 39 (7.69%)	
occurrences (all)	5	4	
ARTHROMYALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
BACK PAIN			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	7 / 41 (17.07%)	3 / 39 (7.69%)	
occurrences (all)	8	3	
BONE PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences (all)	4	2	
BUTTOCK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
CHEST WALL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
CONTUSION RIGHT WRIST			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
CRAMPS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	3 / 39 (7.69%)	
occurrences (all)	1	5	
CRAMPS UPPER LIMB			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HAND CRAMPS,FINGER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
INFLAMMATION TOE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

JOINT STIFFNESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
LEFT ELBOW PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
LESS POWER IN HANDS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
MUSCLE CRAMPS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
MUSCLE SPASM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
MUSCLE WEAKNESS LOWER LIMB			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
MUSCULOSKELETAL CONNECTIVE TISSUE DISORDER-OTHER : GONALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MYALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 41 (9.76%)	5 / 39 (12.82%)	
occurrences (all)	4	7	
NECK PAIN			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	3	2	
OSTEONECROSIS OF JAW			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
OSTEOPOROSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Infections and infestations			
BRONCHIAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 41 (17.07%)	2 / 39 (5.13%)	
occurrences (all)	7	2	
CATHETER RELATED INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CHEST INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
INFECTION (NO DETAILS)			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
INFECTIONS OTHER			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
LARYNGITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
LUNG INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
NAIL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
OTITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PARONYCHIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
PERITONEAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PHARYNGITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
RHINITIS INFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	

SINUSITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
SKIN INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	7 / 39 (17.95%)	
occurrences (all)	1	7	
STREPTOCOCCAL BACTEREMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
TOOTH INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
URINARY TRACT INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 41 (14.63%)	5 / 39 (12.82%)	
occurrences (all)	6	6	
VAGINAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
WOUND INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
BLADDER INFECTION			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	2 / 41 (4.88%)	0 / 39 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
ANOREXIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	17 / 41 (41.46%)	14 / 39 (35.90%)	
occurrences (all)	29	15	
DEFICIENCY OF FOLIC ACID			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
DEHYDRATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HYPERCALCEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HYPERGLYCEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	6	
HYPERURICEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
HYPOCALCEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HYPOGLYCEMIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HYPOKALEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences (all)	4	4	
HYPOMAGNESEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
HYPONATREMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HYPOREXIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
INCREASED LDH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
VITAMIN D DEFICIENCY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2014	Patients considered to have a brain disease progression regardless their response in the peripheral disease were considered as eligible to shift from the combination of pertuzumab plus trastuzumab +/ chemotherapy to the trastuzumab emtansine treatment (second part of the study). However, patients being treated with anti HER2 monoclonal antibodies for metastatic disease seem to suffer from an increased risk of brain metastases, even in cases with responsive peripheral disease (Stemmler et al., 2007). Based on a retrospective review of 122 patients, at the time that brain metastases were identified, in half of patients peripheral systemic disease was either stable or responding to trastuzumab based therapy. Correlation between HER2 overexpression of primary breast cancers and subsequent brain metastases is 97% (Fuchs et al., 2002). Instead, progressive CNS disease probably results from poor penetration of these monoclonal antibodies into the brain, e.g. trastuzumab is a relatively large protein with a molecular weight 148,000. Therefore it would not be expected to cross the blood brain barrier. Based on that, we implemented that those patients that experience progression of brain disease or new brain lesions (of any size and any number) and present a response or stable disease in the peripheral disease can be considered (not obliged) to continue the systemic treatment they were receiving before brain disease progression (PH, PHM or TDM1) after the completion of local CNS treatment (radiation therapy, radiosurgery or equivalent). However, this change affected the dose interruption period that is considered acceptable in the previous version of the protocol. We expect that delays will occur for the patient to complete local CNS treatment and therefore a longer period of delay can be accepted (more than 3 weeks). However, they will need to resume on treatment three weeks at the latest after the day of completion of local treatment for brain disease.

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/29433963

http://www.ncbi.nlm.nih.gov/pubmed/35636341