



## 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  $\geq$  70 years of age, or  $\geq$  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
<b>Arm title</b>	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  $\pm$  10% from baseline. The initial dose of trastuzumab should be administered over 90 ( $\pm$  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 ( $\pm$  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 ( $\pm$  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.

<b>Arm title</b>	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  $\pm$  10% from baseline. The initial dose of trastuzumab should be administered over 90 ( $\pm$  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 ( $\pm$  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 ( $\pm$  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

<b>Arm title</b>	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.

<b>Number of subjects in period 2</b>	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
Lost to follow-up	1
Progressive disease	28

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

<b>Reporting group values</b>	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 <sup>[1]</sup>
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 <sup>[2]</sup>		
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

<b>End point values</b>	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab + metronomic cyclophosphamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 <sup>[3]</sup>	41 <sup>[4]</sup>		
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

<b>End point values</b>	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

<b>End point values</b>	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

<b>End point values</b>	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: -

<b>Serious adverse events</b>	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	
<b>PERIPHERAL ISCHAEMIA</b>			
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	
<b>General disorders and administration site conditions</b>			
<b>SUDDEN DEATH</b>	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	
<b>ASTHENIA</b>			
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	
<b>FATIGUE</b>			
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	
<b>MALAISE</b>			
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	
<b>PYREXIA</b>			
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	
<b>Immune system disorders</b>			
<b>HYPERSENSITIVITY</b>			
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	
<b>ANAPHYLACTIC REACTION</b>			
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	
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>DYSпноEA</b>			
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	
<b>BRONCHOSPASM</b>			
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	
<b>RESPIRATORY FAILURE</b>			
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	
<b>PULMONARY EMBOLISM</b>			
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	
<b>PLEURAL EFFUSION</b>			
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	
<b>LUNG DISORDER</b>			
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	
<b>INTERSTITIAL LUNG DISEASE</b>			
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	
<b>EPISTAXIS</b>			
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	
<b>Psychiatric disorders</b>			
<b>ANXIETY</b>			
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	
<b>CONFUSIONAL STATE</b>			
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	
<b>DELIRIUM</b>			
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	
<b>HALLUCINATION, VISUAL</b>			
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	
<b>Injury, poisoning and procedural complications</b>			
<b>INFUSION RELATED REACTION</b>			
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	
<b>HUMERUS FRACTURE</b>			
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	
<b>HIP FRACTURE</b>			
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	
<b>FALL</b>			
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	
<b>Cardiac disorders</b>			
<b>TACHYCARDIA</b>			
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	
<b>LEFT VENTRICULAR DYSFUNCTION</b>			
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	
<b>CORONARY ARTERY STENOSIS</b>			
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	
<b>CARDIAC FAILURE CONGESTIVE</b>			
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	
<b>CARDIAC FAILURE</b>			
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	
<b>CARDIAC ARREST</b>			
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	
<b>ATRIAL FIBRILLATION</b>			
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	
<b>Nervous system disorders</b>			
<b>COGNITIVE DISORDER</b>			
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	
<b>EPILEPSY</b>			
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	
<b>Blood and lymphatic system disorders</b>			
<b>SPLENIC HAEMORRHAGE</b>			
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	
<b>Ear and labyrinth disorders</b>			
<b>MENIERE'S DISEASE</b>			
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	
<b>Gastrointestinal disorders</b>			
<b>ABDOMINAL PAIN</b>			
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	
<b>SMALL INTESTINAL OBSTRUCTION</b>			
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	
<b>VOMITING</b>			
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	
<b>NAUSEA</b>			
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	
<b>DIARRHOEA</b>			
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	
<b>Hepatobiliary disorders</b>			
<b>CHOLECYSTITIS</b>			
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	
<b>Renal and urinary disorders</b>			
<b>ACUTE KIDNEY INJURY</b>			
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	
<b>ANURIA</b>			
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	
<b>RENAL FAILURE</b>			
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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>BACK PAIN</b>			
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	
<b>GROIN PAIN</b>			
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	
<b>Infections and infestations</b>			
<b>SKIN INFECTION</b>			
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	
<b>PNEUMONIA</b>			
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	
<b>PERITONITIS</b>	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	
<b>INTERVERTEBRAL DISCITIS</b>			
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	
<b>GASTROENTERITIS</b>			
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	
<b>ESCHERICHIA URINARY TRACT INFECTION</b>			
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	
<b>ERYSIPELAS</b>			
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	
<b>CELLULITIS</b>			
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	
<b>BRONCHITIS</b>			
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	
<b>STREPTOCOCCAL BACTERAEMIA</b>			
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	
<b>URINARY TRACT INFECTION</b>			
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	
<b>Metabolism and nutrition disorders</b>			
<b>HYPOGLYCAEMIA</b>			
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	
<b>DEHYDRATION</b>			
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	
<b>CACHEXIA</b>			
alternative dictionary used: MedDRA 24.1	Additional description: Fatal adverse event, occurred during period 2, i.e. after start of T-DM1 treatment		

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 %

<b>Non-serious adverse events</b>	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) MYELOYDYSPLASTIC SYNDROME alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 39 (0.00%) 0
ULCERATING CHARACTER OF BREASTCARCINOMA alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 39 (0.00%) 0
Vascular disorders HYPOTENSIVE SYMPTOMS alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 39 (0.00%) 0
ARTERIAL THROMBOSIS alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 39 (0.00%) 0
HEMATOMA alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	2 / 39 (5.13%) 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

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

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

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

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

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

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

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

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

subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)
occurrences (all)	1	0
<b>ATRIAL FIBRILLATION</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	4 / 41 (9.76%)	1 / 39 (2.56%)
occurrences (all)	6	1
<b>CARDIAC ARREST</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	1
<b>CHEST PAIN - CARDIAC</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	1
<b>EXTRASYSTOLES</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)
occurrences (all)	1	0
<b>HEART FAILURE</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)
occurrences (all)	3	0
<b>LEFT VENTRICULAR SYSTOLIC DYSFUNCTION</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)
occurrences (all)	1	1
<b>MITRAL VALVE DISEASE</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)
occurrences (all)	1	0
<b>PALPITATIONS</b>		
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
<b>EXTRAPYRAMIDAL DISORDER</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	1
<b>HEADACHE</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	6 / 41 (14.63%)	4 / 39 (10.26%)
occurrences (all)	7	5
<b>HYPOESTHESIA</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)
occurrences (all)	1	0
<b>LETHARGY</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)
occurrences (all)	1	1
<b>MEMORY IMPAIRMENT</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)
occurrences (all)	1	1
<b>MIGRAINE</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)
occurrences (all)	4	0
<b>NEURALGIA</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)
occurrences (all)	1	0
<b>NEUROLOGICAL DEGRADATION</b>		
alternative dictionary used: CTCAE 4.0		
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	1

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

subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 39 (2.56%) 1	
Blood and lymphatic system disorders LYMPH NODE PAIN alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 39 (0.00%) 0	
POSSIBLE MYELOPDYPLASIA alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 39 (0.00%) 0	
Ear and labyrinth disorders TINNITUS alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	0 / 39 (0.00%) 0	
BALANCE DISORDER alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 2	0 / 39 (0.00%) 0	
HEARING IMPAIRED alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	1 / 39 (2.56%) 1	
MENIERE'S DISEASE alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 39 (2.56%) 1	
VERTIGO alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	1 / 39 (2.56%) 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	
<b>CONJUNCTIVITIS</b>			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 41 (14.63%)	0 / 39 (0.00%)	
occurrences (all)	7	0	
<b>DRY EYE</b>			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 41 (7.32%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
<b>EYE DISTURBANCES, FLASHING AND ZIGZAG EFFECT (MIGRAINE)</b>			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
<b>EYE MUCOSITIS</b>			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
<b>EYE PAIN</b>			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
<b>WATERING EYES</b>			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
<b>BLURRED VISION</b>			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
<b>Gastrointestinal disorders</b>			
<b>MUCOSITIS ORAL</b>			
alternative dictionary used: CTCAE 4.0			

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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>