



Clinical trial results:

A randomized phase II trial of pertuzumab in combination with trastuzumab with or without chemotherapy, both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer

Summary

EudraCT number	2012-002556-17
Trial protocol	FR DE NL
Global end of trial date	31 May 2020

Results information

Result version number	v1 (current)
This version publication date	19 June 2022
First version publication date	19 June 2022

Trial information

Trial identification

Sponsor protocol code	SAKK22/10/UC-0140/1207
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01835236
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr
Scientific contact	Jerôme Lemonnier, chef de projets, UNICANCER, 33 1 71 93 67 02, j-lemonnier@unicancer.fr
Sponsor organisation name	SAKK
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, CH-3008
Public contact	Sabrina Chiquet, SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH, 41 31 389 91 84, sabrina.chiquet@sakk.ch
Scientific contact	Sabrina Chiquet, SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH, 41 31 389 91 84, sabrina.chiquet@sakk.ch

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	No

1901/2006 apply to this trial?

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 October 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the efficacy in terms of overall survival (OS) at 24 months of a chemotherapy-free dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) and of a chemotherapy-containing dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) in patients with HER2-positive metastatic breast cancer.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Furthermore, independent Ethics Committees reviewed and gave favorable opinions to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.

Written informed consent was obtained from all patients prior to enrollment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	France: 119
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Switzerland: 75
Worldwide total number of subjects	210
EEA total number of subjects	135

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)	126
From 65 to 84 years	84
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pernetta was an international, multicenter, randomized, open label, phase II trial designed to compare the effect of pertuzumab in combination with trastuzumab with or without chemotherapy, both followed by T-DM1 in case of progression, on overall survival at 2 years in patients with HER2-positive metastatic breast cancer.

Pre-assignment

Screening details:

The trial consisted of a screening phase before randomization to establish eligibility, a treatment phase (3-week treatment cycles; 12 cycles), and a long-term follow-up to monitor overall survival, progression-free survival, time to failure of strategy, objective response, disease control, quality of life, and safety.

Period 1

Period 1 title	First-line treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemotherapy-free dual HER2-inbibition

Arm description:

Chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab:

* Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

* Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks untill disease progression at 8 mg/kg by intravenous infusion over 30 to 90 min.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min. Pertuzumab was administered after a 30-minute observation period following the administration of trastuzumab.

Arm title	Chemotherapy-containing dual HER2-inbibition
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Arm description:

Chemotherapy-containing dual HER2-inbibition with trastuzumab and pertuzumab:

HER2-inhibition:

* Trastuzumab first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

PLUS

* Pertuzumab first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Chemotherapy:

* Paclitaxel administrated by intravenous infusion at 90 mg/m² on day 1, 8, and 15 every 4 weeks for ≥4 months.

OR

* Vinorelbine first administrated by intravenous infusion at 25 mg/m² on day 1, 8 then by intravenous infusion at 30 mg/m² on day 1, 8, and 15 every 3 weeks for ≥4 months.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks until disease progression at 8 mg/kg by intravenous infusion over 30 to 90 min.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min. Pertuzumab was administered after a 30-minute observation period following the administration of trastuzumab.

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

Dosage and administration details:

Paclitaxel was administrated by intravenous infusion at 90 mg/m² on day 1, 8, and 15 every 4 weeks for ≥4 months.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Vinorelbine was first administrated by intravenous infusion at 25 mg/m² on day 1, 8 then by intravenous infusion at 30 mg/m² on day 1, 8, and 15 every 3 weeks for ≥4 months.

Number of subjects in period 1	Chemotherapy-free dual HER2-inhibition	Chemotherapy-containing dual HER2-inhibition
Started	105	105
Completed	64	47
Not completed	41	58
Physician decision	7	7
Patient never received treatment	-	2
Secondary malignancy	-	1
HER2 treatment held for >2 administrations	2	1
Sponsor decision	10	13
Consent withdrawn by subject	1	2
Adverse event, non-fatal	4	5
Symptomatic deterioration during 1st-line therapy	3	2
Death	-	1
Unknown	-	2
Radiotherapy of a bone metastasis	-	1
Patient's refusal to continue the treatment	7	9
Symptomatic after PD under 1st-line therapy	-	1
Age-related	-	1
Protocol deviation	7	10

Period 2

Period 2 title	Second-line treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	T-DM1
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Arm description:

Following disease progression under 1st_line treatment, T-DM1 was administrated every 3 weeks until unacceptable toxicity or disease progression at the dose of 3.6 mg/kg by intravenous infusion.

Arm type	Experimental
Investigational medicinal product name	T-DM1
Investigational medicinal product code	
Other name	Kadcyla
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

T-DM1 was administrated at the dose of 3.6 mg/kg by intravenous infusion every 3 weeks until

unacceptable toxicity or disease progression.

Number of subjects in period 2	T-DM1
Started	111
Completed	7
Not completed	104
Physician decision	3
Patient decision	4
Disease progression	75
Adverse event, non-fatal	5
Death	3
Secondary malignancy	2
Symptomatic deterioration under T-DM1	6
Protocol deviation	6

Baseline characteristics

Reporting groups

Reporting group title	Chemotherapy-free dual HER2-inbibition
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Reporting group description:

Chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab:

* Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

* Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

Reporting group title	Chemotherapy-containing dual HER2-inbibition
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Reporting group description:

Chemotherapy-containing dual HER2-inbibition with trastuzumab and pertuzumab:

HER2-inhibition:

* Trastuzumab first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

PLUS

* Pertuzumab first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Chemotherapy:

* Paclitaxel administrated by intravenous infusion at 90 mg/m² on day 1, 8, and 15 every 4 weeks for ≥4 months.

OR

* Vinorelbine first administrated by intravenous infusion at 25 mg/m² on day 1, 8 then by intravenous infusion at 30 mg/m² on day 1, 8, and 15 every 3 weeks for ≥4 months.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

Reporting group values	Chemotherapy-free dual HER2-inbibition	Chemotherapy-containing dual HER2-inbibition	Total
Number of subjects	105	105	210
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	59	57	
full range (min-max)	28 to 85	26 to 81	-
Gender categorical			
Units: Subjects			
Female	105	105	210

Male	0	0	0
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WHO performance status			
Units: Subjects			
ECOG 0	61	66	127
ECOG 1	37	38	75
ECOG 2	7	1	8
Hormone receptor status			
Units: Subjects			
Positive	68	66	134
Negative	37	39	76
Primary metastatic			
Units: Subjects			
Yes	40	36	76
No	65	69	134
Prior chemotherapy			
Units: Subjects			
Yes	53	47	100
No	52	57	109
Missing	0	1	1
Prior anti-HER2 treatment			
Units: Subjects			
Yes	44	42	86
No	61	62	123
Missing	0	1	1
Prior endocrine therapy			
Units: Subjects			
Yes	42	36	78
No	63	68	131
Missing	0	1	1
Weight			
Units: Kg			
median	66	68	
full range (min-max)	33 to 113	43 to 125	-
Height			
Units: cm			
median	162	163	
full range (min-max)	146 to 180	146 to 182	-
Body surface			
Units: m2			
median	1.7	1.7	
full range (min-max)	1.2 to 2.3	1.4 to 2.2	-

End points

End points reporting groups

Reporting group title	Chemotherapy-free dual HER2-inbibition
Reporting group description:	
Chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab:	
* Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.	
* Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.	
Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.	
Reporting group title	Chemotherapy-containing dual HER2-inbibition
Reporting group description:	
Chemotherapy-containing dual HER2-inbibition with trastuzumab and pertuzumab:	
HER2-inhibition:	
* Trastuzumab first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.	
PLUS	
* Pertuzumab first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.	
Chemotherapy:	
* Paclitaxel administrated by intravenous infusion at 90 mg/m2 on day 1, 8, and 15 every 4 weeks for ≥ 4 months.	
OR	
* Vinorelbine first administrated by intravenous infusion at 25 mg/m2 on day 1, 8 then by intravenous infusion at 30 mg/m2 on day 1, 8, and 15 every 3 weeks for ≥ 4 months.	
Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.	
Reporting group title	T-DM1
Reporting group description:	
Following disease progression under 1st_line treatment, T-DM1 was administrated every 3 weeks until unacceptable toxicity or disease progression at the dose of 3.6 mg/kg by intravenous infusion.	

Primary: Overall survival at 24 months

End point title	Overall survival at 24 months ^[1]
End point description:	
The primary objective of this trial was to evaluate the efficacy in terms of overall survival at 24 months of a chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) and of a chemotherapy-containing dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) in patients with HER2-positive metastatic breast cancer.	
End point type	Primary
End point timeframe:	
Overall survival was defined as the amount of patients being alive at least 24 months after randomization.	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Statistical comparisons by hypothesis tests between treatment arms were not planned as the power would be very low.	

End point values	Chemotherapy-free dual HER2-inbibition	Chemotherapy-containing dual HER2-inbibition		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: Percent of patients				
Alive	79	78		
Dead	21	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival of 1st-line treatment ignoring first CNS lesion

End point title	Progression-free survival of 1st-line treatment ignoring first CNS lesion
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End point description:

Progression-free survival (PFS) of first-line treatment ignoring first central nervous system (CNS) lesion was the time from randomization to first event of disease progression (ignoring first CNS lesion event) or death of any cause, whichever occurs first.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, thereafter every 12 weeks during 1st-line treatment.

End point values	Chemotherapy-free dual HER2-inbibition	Chemotherapy-containing dual HER2-inbibition		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: month				
median (confidence interval 95%)	8.4 (7.9 to 12.0)	23.3 (18.9 to 33.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS of second-line treatment

End point title	PFS of second-line treatment
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End point description:

PFS of second-line treatment was defined as the time from registration to second-line treatment to the first event of disease progression during second-line treatment or death of any cause, whichever occurs first.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18

weeks, then every 12 weeks.

End point values	T-DM1			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: month				
median (confidence interval 95%)	6.9 (5.0 to 11.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS of second-line treatment ignoring first CNS lesion

End point title	PFS of second-line treatment ignoring first CNS lesion
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End point description:

PFS of second-line treatment was defined as the time from registration to second-line treatment to the first event of disease progression (ignoring CNS lesion) during second-line treatment or death of any cause, whichever occurs first.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

End point values	T-DM1			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: month				
median (confidence interval 95%)	8.9 (5.3 to 11.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to failure of strategy of first- plus second-line treatment

End point title	Time to failure of strategy of first- plus second-line treatment
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End point description:

Time to failure of strategy (TFS) of first- plus second-line treatment was defined as the time from randomization to a TFS event of first- plus second-line treatment. A TFS event of first- plus second-line treatment was defined as disease progression, CNS progression, or death of any cause, whichever occurred first.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, and every 12 weeks thereafter until disease progression then within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

End point values	Chemotherapy-free dual HER2-inhibition	Chemotherapy-containing dual HER2-inhibition		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: month				
median (confidence interval 95%)	29.0 (18.9 to 63.4)	48.6 (35.8 to 69.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type	Secondary
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End point timeframe:

OS was defined as the time from randomization until death by any cause.

End point values	Chemotherapy-free dual HER2-inhibition	Chemotherapy-containing dual HER2-inhibition		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: month				
median (confidence interval 95%)	60.5 (42.6 to 81)	68.8 (55.3 to 75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response of first-line treatment (based on investigator's assessment)

End point title	Objective response of first-line treatment (based on investigator's assessment)
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End point description:

Objective response (OR) of first-line treatment was defined as the status complete response (CR) or partial response (PR) succeeded as best response during first-line of treatment.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, thereafter every 12 weeks during 1st-line treatment.

End point values	Chemotherapy-free dual HER2-inbibition	Chemotherapy-containing dual HER2-inbibition		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: Percent of patients				
CR	7	25		
PR	38	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control of first-line treatment (based on investigator's assessment)

End point title	Disease control of first-line treatment (based on investigator's assessment)
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End point description:

Disease control (DC) of first-line treatment was defined as the status of response CR, PR or stable disease (SD) for a period of 6 months and no progressive disease (PD) at 6 months after randomization. Patients with SD and last evaluation before 6 months after randomization or no assessment within 6 months after randomization were not considered.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, thereafter every 12 weeks during 1st-line treatment.

End point values	Chemotherapy-free dual HER2-inbibition	Chemotherapy-containing dual HER2-inbibition		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: Percent of patients				
CR	7	25		
PR	38	36		
SD ≥6 months	17	18		

Statistical analyses

No statistical analyses for this end point

Secondary: OR of second-line treatment (based on investigator's assessment)

End point title	OR of second-line treatment (based on investigator's assessment)
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End point description:

OR of second-line treatment was defined as the status of response CR or PR succeeded as best response during second-line of treatment.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

End point values	T-DM1			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: Percent of patients				
CR	8			
PR	21			

Statistical analyses

No statistical analyses for this end point

Secondary: DC of second-line treatment (based on investigator's assessment)

End point title	DC of second-line treatment (based on investigator's assessment)
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End point description:

DC of second-line treatment was defined as the status of response CR, PR or SD for a period of 6 months and no PD at 6 months after registration of second-line treatment. Patients with SD and last evaluation before 6 months after registration to the second-line of treatment or no assessment within 6 months after registration to the second-line of treatment were not considered.

End point type	Secondary
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End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

End point values	T-DM1			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: Percent of patients				
CR	8			
PR	21			
SD ≥6 months	17			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment (up to 7 years).

Adverse event reporting additional description:

For non-serious adverse events, the number of occurrences were not recorded, the number of patient affected were the only value available. Thus, the number of patient affected was entered in both "Subjects affected number" and "Occurrence all number" fields.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Chemotherapy-free dual HER2-inbibition
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Reporting group description: -

Reporting group title	Chemotherapy-containing dual HER2-inbibition
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Reporting group description: -

Reporting group title	Second-line therapy
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Reporting group description: -

Serious adverse events	Chemotherapy-free dual HER2-inbibition	Chemotherapy-containing dual HER2-inbibition	Second-line therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 105 (43.81%)	37 / 103 (35.92%)	38 / 111 (34.23%)
number of deaths (all causes)	33	26	39
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basalioma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast angiosarcoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Leiomyomas of the uterus			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic event	Additional description: 1		
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Adnexectomy			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast conserving surgery with ALND			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hallux valgus requiring surgery subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Persistent exulceration of primary tumor requiring palliative ablation subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary lobectomy (L) with hilar and mediastinal adenectomy subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spine surgery subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 105 (1.90%)	1 / 103 (0.97%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurologic symptom			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reduced general condition			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	4 / 105 (3.81%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic organ prolapse			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic pain			

subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
AST and ALT increased			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	3 / 111 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 105 (0.00%)	2 / 103 (1.94%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Ankle fracture			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cranio-cerebral injury			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral compression fracture			

subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
3-vessel coronary disease			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Transient ischemic attacks			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 105 (0.00%)	3 / 103 (2.91%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic nerve disorder			

subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 105 (1.90%)	4 / 103 (3.88%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	2 / 2	1 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 105 (1.90%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle cramps generalized			

subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathologic bone fracture			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 lung infection			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter-related infection			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis infective			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			

subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 105 (0.95%)	2 / 103 (1.94%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purulent pleurisy			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylodiscitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	12 / 111 (10.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval infection			

subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 105 (0.00%)	2 / 103 (1.94%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

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

Non-serious adverse events	Chemotherapy-free dual HER2-inhibition	Chemotherapy-containing dual HER2-inhibition	Second-line therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 105 (100.00%)	103 / 103 (100.00%)	111 / 111 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	6 / 105 (5.71%)	3 / 103 (2.91%)	4 / 111 (3.60%)
occurrences (all)	6	3	4
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 105 (3.81%)	7 / 103 (6.80%)	2 / 111 (1.80%)
occurrences (all)	4	7	2
Hot flush			
subjects affected / exposed	19 / 105 (18.10%)	10 / 103 (9.71%)	13 / 111 (11.71%)
occurrences (all)	19	10	13
Hypertension			
subjects affected / exposed	100 / 105 (95.24%)	102 / 103 (99.03%)	104 / 111 (93.69%)
occurrences (all)	100	102	104
General disorders and administration site conditions			
Chills			
subjects affected / exposed	8 / 105 (7.62%)	7 / 103 (6.80%)	7 / 111 (6.31%)
occurrences (all)	8	7	7
Oedema limbs			

subjects affected / exposed	9 / 105 (8.57%)	15 / 103 (14.56%)	12 / 111 (10.81%)
occurrences (all)	9	15	12
Fatigue			
subjects affected / exposed	60 / 105 (57.14%)	81 / 103 (78.64%)	79 / 111 (71.17%)
occurrences (all)	60	81	79
Fever			
subjects affected / exposed	24 / 105 (22.86%)	22 / 103 (21.36%)	10 / 111 (9.01%)
occurrences (all)	24	22	10
Flu like symptoms			
subjects affected / exposed	18 / 105 (17.14%)	14 / 103 (13.59%)	10 / 111 (9.01%)
occurrences (all)	18	14	10
Non-cardiac chest pain			
subjects affected / exposed	3 / 105 (2.86%)	9 / 103 (8.74%)	3 / 111 (2.70%)
occurrences (all)	3	9	3
Pain			
subjects affected / exposed	22 / 105 (20.95%)	32 / 103 (31.07%)	18 / 111 (16.22%)
occurrences (all)	22	32	18
Pharyngitis			
subjects affected / exposed	4 / 105 (3.81%)	10 / 103 (9.71%)	2 / 111 (1.80%)
occurrences (all)	4	10	2
Immune system disorders			
Allergic reaction			
subjects affected / exposed	15 / 105 (14.29%)	10 / 103 (9.71%)	3 / 111 (2.70%)
occurrences (all)	15	10	3
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	4 / 105 (3.81%)	6 / 103 (5.83%)	6 / 111 (5.41%)
occurrences (all)	4	6	6
Respiratory, thoracic and mediastinal disorders			
Allergic rhinitis			
subjects affected / exposed	11 / 105 (10.48%)	16 / 103 (15.53%)	8 / 111 (7.21%)
occurrences (all)	11	16	8
Cough			
subjects affected / exposed	22 / 105 (20.95%)	23 / 103 (22.33%)	19 / 111 (17.12%)
occurrences (all)	22	23	19
Dyspnoea			

subjects affected / exposed occurrences (all)	34 / 105 (32.38%) 34	23 / 103 (22.33%) 23	27 / 111 (24.32%) 27
Epistaxis subjects affected / exposed occurrences (all)	16 / 105 (15.24%) 16	24 / 103 (23.30%) 24	19 / 111 (17.12%) 19
Voice alteration subjects affected / exposed occurrences (all)	4 / 105 (3.81%) 4	7 / 103 (6.80%) 7	1 / 111 (0.90%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	9 / 105 (8.57%) 9	7 / 103 (6.80%) 7	7 / 111 (6.31%) 7
Depression subjects affected / exposed occurrences (all)	7 / 105 (6.67%) 7	14 / 103 (13.59%) 14	11 / 111 (9.91%) 11
Insomnia subjects affected / exposed occurrences (all)	21 / 105 (20.00%) 21	16 / 103 (15.53%) 16	11 / 111 (9.91%) 11
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	41 / 105 (39.05%) 41	66 / 103 (64.08%) 66	76 / 111 (68.47%) 76
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	52 / 105 (49.52%) 52	54 / 103 (52.43%) 54	64 / 111 (57.66%) 64
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	53 / 105 (50.48%) 53	66 / 103 (64.08%) 66	96 / 111 (86.49%) 96
Blood bilirubin increased subjects affected / exposed occurrences (all)	13 / 105 (12.38%) 13	11 / 103 (10.68%) 11	17 / 111 (15.32%) 17
Creatinine urine increased subjects affected / exposed occurrences (all)	34 / 105 (32.38%) 34	34 / 103 (33.01%) 34	30 / 111 (27.03%) 30
Ejection fraction decreased			

subjects affected / exposed occurrences (all)	10 / 105 (9.52%) 10	8 / 103 (7.77%) 8	1 / 111 (0.90%) 1
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	6 / 105 (5.71%) 6	7 / 103 (6.80%) 7	16 / 111 (14.41%) 16
Lymphocyte count decreased subjects affected / exposed occurrences (all)	7 / 105 (6.67%) 7	6 / 103 (5.83%) 6	4 / 111 (3.60%) 4
Neutrophil count decreased subjects affected / exposed occurrences (all)	19 / 105 (18.10%) 19	59 / 103 (57.28%) 59	28 / 111 (25.23%) 28
Platelet count decreased subjects affected / exposed occurrences (all)	15 / 105 (14.29%) 15	25 / 103 (24.27%) 25	76 / 111 (68.47%) 76
Weight gain subjects affected / exposed occurrences (all)	33 / 105 (31.43%) 33	32 / 103 (31.07%) 32	19 / 111 (17.12%) 19
Weight loss subjects affected / exposed occurrences (all)	38 / 105 (36.19%) 38	58 / 103 (56.31%) 58	54 / 111 (48.65%) 54
Injury, poisoning and procedural complications Fracture subjects affected / exposed occurrences (all)	2 / 105 (1.90%) 2	6 / 103 (5.83%) 6	2 / 111 (1.80%) 2
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	10 / 105 (9.52%) 10	16 / 103 (15.53%) 16	6 / 111 (5.41%) 6
Dysesthesia subjects affected / exposed occurrences (all)	5 / 105 (4.76%) 5	11 / 103 (10.68%) 11	9 / 111 (8.11%) 9
Dysgeusia subjects affected / exposed occurrences (all)	15 / 105 (14.29%) 15	20 / 103 (19.42%) 20	10 / 111 (9.01%) 10
Headache			

subjects affected / exposed occurrences (all)	25 / 105 (23.81%) 25	31 / 103 (30.10%) 31	21 / 111 (18.92%) 21
Paraesthesia subjects affected / exposed occurrences (all)	13 / 105 (12.38%) 13	34 / 103 (33.01%) 34	16 / 111 (14.41%) 16
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	2 / 105 (1.90%) 2	5 / 103 (4.85%) 5	7 / 111 (6.31%) 7
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	14 / 105 (13.33%) 14	36 / 103 (34.95%) 36	24 / 111 (21.62%) 24
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	48 / 105 (45.71%) 48	86 / 103 (83.50%) 86	69 / 111 (62.16%) 69
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	10 / 105 (9.52%) 10	10 / 103 (9.71%) 10	8 / 111 (7.21%) 8
Eye disorders Blurred vision subjects affected / exposed occurrences (all)	2 / 105 (1.90%) 2	7 / 103 (6.80%) 7	2 / 111 (1.80%) 2
Dry eye subjects affected / exposed occurrences (all)	9 / 105 (8.57%) 9	9 / 103 (8.74%) 9	8 / 111 (7.21%) 8
Watering eyes subjects affected / exposed occurrences (all)	5 / 105 (4.76%) 5	11 / 103 (10.68%) 11	9 / 111 (8.11%) 9
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	18 / 105 (17.14%) 18	24 / 103 (23.30%) 24	11 / 111 (9.91%) 11
Constipation subjects affected / exposed occurrences (all)	15 / 105 (14.29%) 15	29 / 103 (28.16%) 29	26 / 111 (23.42%) 26
Diarrhoea			

subjects affected / exposed	60 / 105 (57.14%)	77 / 103 (74.76%)	26 / 111 (23.42%)
occurrences (all)	60	77	26
Dry mouth			
subjects affected / exposed	3 / 105 (2.86%)	3 / 103 (2.91%)	11 / 111 (9.91%)
occurrences (all)	3	3	11
Dyspepsia			
subjects affected / exposed	8 / 105 (7.62%)	14 / 103 (13.59%)	7 / 111 (6.31%)
occurrences (all)	8	14	7
Dysphagia			
subjects affected / exposed	8 / 105 (7.62%)	6 / 103 (5.83%)	2 / 111 (1.80%)
occurrences (all)	8	6	2
Gastritis			
subjects affected / exposed	6 / 105 (5.71%)	8 / 103 (7.77%)	4 / 111 (3.60%)
occurrences (all)	6	8	4
Gastroesophageal reflux disease			
subjects affected / exposed	10 / 105 (9.52%)	10 / 103 (9.71%)	7 / 111 (6.31%)
occurrences (all)	10	10	7
Haemorrhoids			
subjects affected / exposed	5 / 105 (4.76%)	6 / 103 (5.83%)	2 / 111 (1.80%)
occurrences (all)	5	6	2
Mucositis oral			
subjects affected / exposed	12 / 105 (11.43%)	30 / 103 (29.13%)	9 / 111 (8.11%)
occurrences (all)	12	30	9
Nausea			
subjects affected / exposed	34 / 105 (32.38%)	42 / 103 (40.78%)	39 / 111 (35.14%)
occurrences (all)	34	42	39
Vomiting			
subjects affected / exposed	12 / 105 (11.43%)	16 / 103 (15.53%)	8 / 111 (7.21%)
occurrences (all)	12	16	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 105 (7.62%)	36 / 103 (34.95%)	12 / 111 (10.81%)
occurrences (all)	8	36	12
Dry skin			
subjects affected / exposed	16 / 105 (15.24%)	26 / 103 (25.24%)	13 / 111 (11.71%)
occurrences (all)	16	26	13

Erythema			
subjects affected / exposed	7 / 105 (6.67%)	5 / 103 (4.85%)	6 / 111 (5.41%)
occurrences (all)	7	5	6
Nail loss			
subjects affected / exposed	5 / 105 (4.76%)	11 / 103 (10.68%)	5 / 111 (4.50%)
occurrences (all)	5	11	5
Pruritus			
subjects affected / exposed	15 / 105 (14.29%)	25 / 103 (24.27%)	10 / 111 (9.01%)
occurrences (all)	15	25	10
Rash acneiform			
subjects affected / exposed	11 / 105 (10.48%)	23 / 103 (22.33%)	3 / 111 (2.70%)
occurrences (all)	11	23	3
Rash maculo-papular			
subjects affected / exposed	11 / 105 (10.48%)	13 / 103 (12.62%)	5 / 111 (4.50%)
occurrences (all)	11	13	5
Endocrine disorders			
Conjunctivitis			
subjects affected / exposed	8 / 105 (7.62%)	10 / 103 (9.71%)	9 / 111 (8.11%)
occurrences (all)	8	10	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 105 (15.24%)	25 / 103 (24.27%)	16 / 111 (14.41%)
occurrences (all)	16	25	16
Back pain			
subjects affected / exposed	17 / 105 (16.19%)	16 / 103 (15.53%)	20 / 111 (18.02%)
occurrences (all)	17	16	20
Bone pain			
subjects affected / exposed	15 / 105 (14.29%)	16 / 103 (15.53%)	16 / 111 (14.41%)
occurrences (all)	15	16	16
Flank pain			
subjects affected / exposed	3 / 105 (2.86%)	6 / 103 (5.83%)	3 / 111 (2.70%)
occurrences (all)	3	6	3
Myalgia			
subjects affected / exposed	14 / 105 (13.33%)	26 / 103 (25.24%)	15 / 111 (13.51%)
occurrences (all)	14	26	15
Neck pain			

subjects affected / exposed occurrences (all)	7 / 105 (6.67%) 7	9 / 103 (8.74%) 9	2 / 111 (1.80%) 2
Cramp subjects affected / exposed occurrences (all)	9 / 105 (8.57%) 9	24 / 103 (23.30%) 24	8 / 111 (7.21%) 8
Pain in extremity subjects affected / exposed occurrences (all)	11 / 105 (10.48%) 11	16 / 103 (15.53%) 16	12 / 111 (10.81%) 12
Infections and infestations			
Bladder infection subjects affected / exposed occurrences (all)	2 / 105 (1.90%) 2	8 / 103 (7.77%) 8	1 / 111 (0.90%) 1
Bronchial infection subjects affected / exposed occurrences (all)	9 / 105 (8.57%) 9	3 / 103 (2.91%) 3	3 / 111 (2.70%) 3
Paronychia subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1	9 / 103 (8.74%) 9	2 / 111 (1.80%) 2
Rhinitis infective subjects affected / exposed occurrences (all)	11 / 105 (10.48%) 11	11 / 103 (10.68%) 11	3 / 111 (2.70%) 3
Skin infection subjects affected / exposed occurrences (all)	9 / 105 (8.57%) 9	11 / 103 (10.68%) 11	4 / 111 (3.60%) 4
Upper respiratory infection subjects affected / exposed occurrences (all)	12 / 105 (11.43%) 12	14 / 103 (13.59%) 14	9 / 111 (8.11%) 9
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 105 (4.76%) 5	17 / 103 (16.50%) 17	5 / 111 (4.50%) 5
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	27 / 105 (25.71%) 27	19 / 103 (18.45%) 19	27 / 111 (24.32%) 27
Hypokalaemia			

subjects affected / exposed	2 / 105 (1.90%)	6 / 103 (5.83%)	3 / 111 (2.70%)
occurrences (all)	2	6	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A rather good prognosis population included with a greater proportion of patients with primary metastatic disease and less prior adjuvant/neoadjuvant pretreatment like anti-HER2 and endocrine therapy.
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Notes: