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A Study of Trastuzumab Emtansine (Trastuzumab-MCC-DM1, T-DM1) in Combination With Pertuzumab Administered to Patients With Human Epidermal Growth Factor Receptor-2 (HER2)-Positive Locally Advanced or Metastatic Breast Cancer Who Have Previously Received Trastuzumab

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	Roche Pharma AG
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00875979

Purpose

This was a multi-institutional, multinational, open-label, single-arm Phase Ib/II study designed to evaluate the safety, tolerability, pharmacokinetics, and efficacy of trastuzumab emtansine (trastuzumab-MCC-DM1) administered by intravenous (IV) infusion in combination with pertuzumab in patients with human epidermal growth factor receptor-2 (HER2)-positive locally advanced or metastatic breast cancer who had previously received trastuzumab.

Condition	Intervention	Phase
Metastatic Breast Cancer	Drug: Trastuzumab emtansine [Kadcyla] 3.0 mg/kg Drug: Trastuzumab emtansine [Kadcyla] 3.6 mg/kg Drug: Pertuzumab 420 mg	Phase 1/ Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study

Official Title: A Phase Ib/II, Open-label Study of the Safety, Tolerability, and Efficacy of Trastuzumab Emtansine (Trastuzumab-MCC-DM1, T-DM1) in Combination With Pertuzumab Administered Intravenously to Patients With Human Epidermal Growth Factor Receptor-2 (HER2)-Positive Locally Advanced or Metastatic Breast Cancer Who Have Previously Received Trastuzumab

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [Time Frame: Baseline through the end of the study (up to 2 years 3 months)] [Designated as safety issue: No]

  A patient had an objective response if they had a complete response or a partial response on 2 consecutive occasions ≥ 4 weeks apart. For target lesions, a complete response was defined as the disappearance of all target lesions; a partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. For non-target lesions, a complete response was defined as the disappearance of all non-target lesions; a partial response was defined as the persistence of 1 or more non-target lesions.

Secondary Outcome Measures:

- Duration of Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [Time Frame: Baseline through the end of the study (up to 2 years 3 months)] [Designated as safety issue: No]

  Duration of objective response was defined as the time from initial response to disease progression (PD) or death from any cause. For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements by imaging techniques or clinically. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions.
- Progression-free Survival Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [Time Frame: Baseline through the end of the study (up to 2 years 3 months)] [Designated as safety issue: No]

  Progression-free survival was defined as the time from randomization to first documented disease progression (PD) or death due to any cause within 30 days of the last treatment, whichever occurred first. For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements by imaging techniques or clinically. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions.

Enrollment: 67
Study Start Date: May 2009
Primary Completion Date: August 2011
Study Completion Date: August 2011

Arms	Assigned Interventions
Experimental: Trastuzumab emtansine 3.0 mg/kg + pertuzumab 420 mg Patients received trastuzumab emtansine 3.0 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of	Drug: Trastuzumab emtansine [Kadcyla] 3.0 mg/kg Trastuzumab emtansine was provided as a single-use lyophilized formulation. Other Names: trastuzumab-DM1 trastuzumab-MCC-DM1

Arms	Assigned Interventions
another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.	T-DM1 Drug: Pertuzumab 420 mg Pertuzumab was provided as a single-use formulation. Other Names: Perjeta
Experimental: Trastuzumab emtansine 3.6 mg/kg + pertuzumab 420 mg Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.	Drug: Trastuzumab emtansine [Kadcyla] 3.6 mg/kg Trastuzumab emtansine was provided as a single-use lyophilized formulation. Other Names: trastuzumab-DM1 trastuzumab-MCC-DM1 T-DM1 Drug: Pertuzumab 420 mg Pertuzumab was provided as a single-use formulation. Other Names: Perjeta

Detailed Description:

There were 2 phases in the study, a Dose Escalation phase (Phase 1b) and a Dose Expansion phase (Phase 2a). In the Dose Escalation phase, 3 patients were enrolled at the first dose level (3.0 mg/kg trastuzumab emtansine) and and 6 patients were enrolled at the second dose level (3.6 mg/kg trastuzumab emtansine). An additional 58 patients were enrolled at the 3.6 mg/kg trastuzumab emtansine dose level in the Dose Expansion phase (Phase 2a) of the study.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Histologically documented human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic breast cancer.
- Tumor tissue blocks or 15-20 unstained tissue slides for confirmatory central laboratory HER2 status testing and other exploratory assessments.
- Prior trastuzumab in any line of therapy.
- No prior trastuzumab emtansine (T-DM1) or pertuzumab therapy.
- Measurable disease.
- For women of childbearing potential, agreement to use an effective form of contraception and to continue its use for the duration of the study.
- Life expectancy ≥ 90 days.

Exclusion Criteria:

- Less than 21 days since the last anti-tumor therapy, including chemotherapy, biologic, experimental, immune, hormonal, or radiotherapy for the treatment of breast cancer, with the following exceptions: Hormone-replacement therapy or oral contraceptives; palliative radiation therapy involving ≤ 25% of marrow-bearing bone if administered ≥ 14 days prior to first study treatment.
- History of intolerance or hypersensitivity to trastuzumab and/or adverse events related to trastuzumab that resulted in trastuzumab being permanently discontinued.
- Peripheral neuropathy of Grade ≥ 2.
- History of clinically significant cardiac dysfunction.
- Current severe, uncontrolled systemic disease, eg, clinically significant cardiovascular, pulmonary, or metabolic disease.
- Brain metastases that are untreated, progressive, or have required any type of therapy to control symptoms from brain metastases within 60 days of the first study treatment.
- History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or other malignancy with a similar expected curative outcome.

Contacts and Locations

Locations

United States, Florida
Boca Raton, Florida, United States, 33428
Deerfield Beach, Florida, United States, 33442
United States, Illinois
Maywood, Illinois, United States, 60153
United States, Indiana
Indianapolis, Indiana, United States, 46202
United States, Kansas
Wichita, Kansas, United States, 67214
United States, Maryland
Rockville, Maryland, United States, 20850-3348
United States, North Carolina
Chapel Hill, North Carolina, United States, 27514
United States, Pennsylvania
Philadelphia, Pennsylvania, United States, 19104
Philadelphia, Pennsylvania, United States, 19111
United States, Tennessee
Nashville, Tennessee, United States, 37203
Belgium
Bruxelles, Belgium, 1000
Canada, British Columbia
Vancouver, British Columbia, Canada, V5Z 1H5
Canada, Quebec
Montreal, Quebec, Canada, H3A 1A1
France
Paris, France, 75248
Villejuif, France, 94805

Germany
Köln, Germany, 50924
Italy
Aviano, Italy, 33081
Milano, Italy, 20133
Spain
Barcelona, Spain, 08035
Valencia, Spain, 46010

Investigators

Study Director:	Elaine K. Wong, M.Sc., M.D.	Genentech, Inc.

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	BO22495 TDM4373g [Genentech]
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	There were 2 phases in the study, a Dose Escalation phase (Phase 1b) and a Dose Expansion phase (Phase 2a).

Reporting Groups

	Description
Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.0 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.
Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.

Dose Escalation Phase - 3.0 mg/kg

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
Started	3	0
Completed	0	0
Not Completed	3	0
Disease Progression	1	0
Physician Decision	1	0
Patient/Legal Guardian Decision	1	0

Dose Escalation Phase - 3.6 mg/kg

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
Started	0	6
Completed	0	0
Not Completed	0	6
Disease Progression	0	6

Dose Expansion Phase - 3.6 mg/kg

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
Started	0	58
Completed	0	11
Not Completed	0	47
Disease Progression	0	37
Physician Decision	0	3
Patient/legal Guardian Decision	0	3
Started Non-protocol Anti-Cancer Therapy	0	3
Death	0	1

Baseline Characteristics

Analysis Population Description

Treated population: All patients who received at least 1 dose of study drug and had at least 1 follow-up tumor assessment.

Reporting Groups

	Description
Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.0 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.
Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.

Baseline Measures

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg	Total
Number of Participants	3	64	67
Age, Continuous [units: years] Mean (Standard Deviation)	53.3 (1.5)	52.7 (10.8)	52.7 (10.5)
Gender, Male/Female [units: participants]			
Female	3	63	66
Male	0	1	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST)
Measure Description	A patient had an objective response if they had a complete response or a partial response on 2 consecutive occasions ≥ 4 weeks apart. For target lesions, a complete response was defined as the disappearance of all target lesions; a partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. For non-target lesions, a complete response was defined as the disappearance of all non-target lesions; a partial response was defined as the persistence of 1 or more non-target lesions.

Time Frame	Baseline through the end of the study (up to 2 years 3 months)
Safety Issue?	No

Analysis Population Description

Treated population: All enrolled patients who had baseline measureable disease.

Reporting Groups

	Description
Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.0 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.
Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.

Measured Values

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
Number of Participants Analyzed	3	64
Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [units: Percentage of patients] Number (95% Confidence Interval)	66.7 (13.5 to 98.3)	40.6 (28.5 to 53.6)

2. Secondary Outcome Measure:

Measure Title	Duration of Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST)

Measure Description	Duration of objective response was defined as the time from initial response to disease progression (PD) or death from any cause. For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements by imaging techniques or clinically. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions.
Time Frame	Baseline through the end of the study (up to 2 years 3 months)
Safety Issue?	No

Analysis Population Description

Treated population: All enrolled patients who had baseline measureable disease. Only patients with an objective response were included in the analysis.

Reporting Groups

	Description
Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.0 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.
Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.

Measured Values

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
Number of Participants Analyzed	2	26
Duration of Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [units: Months] Median (95% Confidence Interval)	8.6 (NA to NA) [1]	13.9 (6.93 to NA) [2]

[1] The confidence interval could not be estimated due to the small sample size.

[2] The upper limit of the confidence interval could not be estimated due to the small sample size.

3. Secondary Outcome Measure:

Measure Title	Progression-free Survival Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST)
Measure Description	Progression-free survival was defined as the time from randomization to first documented disease progression (PD) or death due to any cause within 30 days of the last treatment, whichever occurred first. For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements by imaging techniques or clinically. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions.
Time Frame	Baseline through the end of the study (up to 2 years 3 months)
Safety Issue?	No

Analysis Population Description

Treated population: All enrolled patients.

Reporting Groups

	Description
Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.0 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.
Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.

Measured Values

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
Number of Participants Analyzed	3	64
Progression-free Survival Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [units: Months] Median (95% Confidence Interval)	13.8 (NA to NA) [1]	6.6 (4.21 to 9.46)

[1] The confidence interval could not be estimated due to the small sample size.

Reported Adverse Events

Time Frame	From informed consent until treatment start (T), serious adverse events (SAE) related to protocol procedures were reported. From the start up to 30 days after the end of T, all AEs and SAEs were reported. Thereafter, only T-related SAEs were reported.
Additional Description	Safety population: All patients who received at least 1 dose of study drug.

Reporting Groups

	Description
Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.0 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.
Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of every 3 week cycle until progressive disease, intolerable toxicity, initiation of another anti-cancer therapy, or patient discontinuation. Patients also received a loading dose of 840 mg of pertuzumab IV on Day 1 of Cycle 1 followed by pertuzumab 420 mg IV on Day 1 of every subsequent 3 week cycle.

Serious Adverse Events

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/3 (0%)	22/64 (34.38%)
Cardiac disorders		
Pericardial effusion [A] †	0/3 (0%)	1/64 (1.56%)
Tachycardia [A] †	0/3 (0%)	1/64 (1.56%)
Gastrointestinal disorders		
Abdominal pain [A] †	0/3 (0%)	2/64 (3.12%)
Colitis [A] †	0/3 (0%)	1/64 (1.56%)
Diarrhoea [A] †	0/3 (0%)	1/64 (1.56%)

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Gastritis [A] †	0/3 (0%)	1/64 (1.56%)
Ileus [A] †	0/3 (0%)	1/64 (1.56%)
Nausea [A] †	0/3 (0%)	2/64 (3.12%)
Vomiting [A] †	0/3 (0%)	2/64 (3.12%)
General disorders		
Fatigue [A] †	0/3 (0%)	1/64 (1.56%)
Pain [A] †	0/3 (0%)	1/64 (1.56%)
Pyrexia [A] †	0/3 (0%)	1/64 (1.56%)
Hepatobiliary disorders		
Hepatic cirrhosis [A] †	0/3 (0%)	1/64 (1.56%)
Infections and infestations		
Breast cellulitis [A] †	0/3 (0%)	1/64 (1.56%)
Cellulitis [A] †	0/3 (0%)	3/64 (4.69%)
Localised infection [A] †	0/3 (0%)	1/64 (1.56%)
Osteomyelitis [A] †	0/3 (0%)	1/64 (1.56%)
Pneumonia [A] †	0/3 (0%)	3/64 (4.69%)
Skin infection [A] †	0/3 (0%)	1/64 (1.56%)
Staphylococcal bacteraemia [A] †	0/3 (0%)	1/64 (1.56%)
Urinary tract infection [A] †	0/3 (0%)	1/64 (1.56%)
Metabolism and nutrition disorders		
Diabetic foot [A] †	0/3 (0%)	1/64 (1.56%)
Failure to thrive [A] †	0/3 (0%)	1/64 (1.56%)

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour haemorrhage [A] †	0/3 (0%)	1/64 (1.56%)
Nervous system disorders		
Aphasia [A] †	0/3 (0%)	1/64 (1.56%)
Ataxia [A] †	0/3 (0%)	1/64 (1.56%)
Cerebral haemorrhage [A] †	0/3 (0%)	1/64 (1.56%)
Renal and urinary disorders		
Haematuria [A] †	0/3 (0%)	1/64 (1.56%)
Renal failure acute [A] †	0/3 (0%)	1/64 (1.56%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea [A] †	0/3 (0%)	3/64 (4.69%)
Pleural effusion [A] †	0/3 (0%)	3/64 (4.69%)
Pneumonitis [A] †	0/3 (0%)	1/64 (1.56%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (12.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Total	3/3 (100%)	64/64 (100%)
Blood and lymphatic system disorders		
Anaemia [A] †	2/3 (66.67%)	7/64 (10.94%)
Neutropenia [A] †	0/3 (0%)	5/64 (7.81%)

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Thrombocytopenia [A] †	0/3 (0%)	21/64 (32.81%)
Eye disorders		
Dry eye [A] †	0/3 (0%)	4/64 (6.25%)
Lacrimation increased [A] †	1/3 (33.33%)	5/64 (7.81%)
Gastrointestinal disorders		
Abdominal pain [A] †	0/3 (0%)	7/64 (10.94%)
Abdominal pain upper [A] †	0/3 (0%)	4/64 (6.25%)
Constipation [A] †	1/3 (33.33%)	21/64 (32.81%)
Diarrhoea [A] †	1/3 (33.33%)	25/64 (39.06%)
Dry mouth [A] †	1/3 (33.33%)	6/64 (9.38%)
Dyspepsia [A] †	1/3 (33.33%)	11/64 (17.19%)
Gingival bleeding [A] †	0/3 (0%)	6/64 (9.38%)
Nausea [A] †	2/3 (66.67%)	32/64 (50%)
Vomiting [A] †	0/3 (0%)	18/64 (28.12%)
General disorders		
Asthenia [A] †	1/3 (33.33%)	11/64 (17.19%)
Chest pain [A] †	0/3 (0%)	4/64 (6.25%)
Chills [A] †	2/3 (66.67%)	20/64 (31.25%)
Fatigue [A] †	3/3 (100%)	39/64 (60.94%)
Influenza like illness [A] †	0/3 (0%)	4/64 (6.25%)
Mucosal inflammation [A] †	0/3 (0%)	16/64 (25%)
Oedema peripheral [A] †	0/3 (0%)	7/64 (10.94%)

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Pyrexia [A] †	1/3 (33.33%)	19/64 (29.69%)
Infections and infestations		
Cellulitis [A] †	0/3 (0%)	4/64 (6.25%)
Sinusitis [A] †	0/3 (0%)	5/64 (7.81%)
Upper respiratory tract infection [A] †	0/3 (0%)	5/64 (7.81%)
Urinary tract infection [A] †	0/3 (0%)	8/64 (12.5%)
Injury, poisoning and procedural complications		
Contusion [A] †	0/3 (0%)	4/64 (6.25%)
Investigations		
Alanine aminotransferase increased [A] †	0/3 (0%)	18/64 (28.12%)
Aspartate aminotransferase increased [A] †	0/3 (0%)	19/64 (29.69%)
Blood alkaline phosphatase increased [A] †	0/3 (0%)	6/64 (9.38%)
Blood bilirubin increased [A] †	0/3 (0%)	4/64 (6.25%)
Haemoglobin decreased [A] †	0/3 (0%)	4/64 (6.25%)
Metabolism and nutrition disorders		
Decreased appetite [A] †	2/3 (66.67%)	22/64 (34.38%)
Hypokalaemia [A] †	0/3 (0%)	6/64 (9.38%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	1/3 (33.33%)	13/64 (20.31%)
Back pain [A] †	0/3 (0%)	9/64 (14.06%)
Bone pain [A] †	0/3 (0%)	5/64 (7.81%)
Muscle spasms [A] †	0/3 (0%)	13/64 (20.31%)

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Musculoskeletal chest pain [A] †	0/3 (0%)	4/64 (6.25%)
Musculoskeletal pain [A] †	0/3 (0%)	10/64 (15.62%)
Myalgia [A] †	1/3 (33.33%)	7/64 (10.94%)
Neck pain [A] †	0/3 (0%)	6/64 (9.38%)
Pain in extremity [A] †	0/3 (0%)	12/64 (18.75%)
Nervous system disorders		
Dizziness [A] †	0/3 (0%)	7/64 (10.94%)
Dysgeusia [A] †	2/3 (66.67%)	16/64 (25%)
Headache [A] †	2/3 (66.67%)	16/64 (25%)
Neuropathy peripheral [A] †	0/3 (0%)	7/64 (10.94%)
Peripheral sensory neuropathy [A] †	1/3 (33.33%)	16/64 (25%)
Psychiatric disorders		
Anxiety [A] †	0/3 (0%)	5/64 (7.81%)
Depression [A] †	1/3 (33.33%)	9/64 (14.06%)
Insomnia [A] †	0/3 (0%)	15/64 (23.44%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	1/3 (33.33%)	24/64 (37.5%)
Dysphonia [A] †	0/3 (0%)	6/64 (9.38%)
Dyspnoea [A] †	2/3 (66.67%)	14/64 (21.88%)
Epistaxis [A] †	2/3 (66.67%)	16/64 (25%)
Rhinorrhoea [A] †	1/3 (33.33%)	7/64 (10.94%)
Skin and subcutaneous tissue disorders		

	Trastuzumab Emtansine 3.0 mg/kg + Pertuzumab 420 mg	Trastuzumab Emtansine 3.6 mg/kg + Pertuzumab 420 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Alopecia [A] †	0/3 (0%)	7/64 (10.94%)
Nail disorder [A] †	0/3 (0%)	5/64 (7.81%)
Pruritus [A] †	1/3 (33.33%)	10/64 (15.62%)
Rash [A] †	1/3 (33.33%)	15/64 (23.44%)
Vascular disorders		
Hypertension [A] †	0/3 (0%)	7/64 (10.94%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (12.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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