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A Study of the Efficacy and Safety of Trastuzumab Emtansine (Trastuzumab-MCC-DM1) vs. Trastuzumab (Herceptin®) and Docetaxel (Taxotere®) in Patients With Metastatic HER2-positive Breast Cancer Who Have Not Received Prior Chemotherapy for Metastatic Disease

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00679341

Purpose

This was a Phase II, randomized, multicenter, international, 2-arm, open-label clinical trial designed to explore the efficacy and safety of trastuzumab emtansine (T-DM1) relative to the combination of trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced breast cancer and/or metastatic breast cancer who have not received prior chemotherapy for metastatic disease.

Condition	Intervention	Phase
Breast Cancer	Drug: Trastuzumab emtansine [Kadcyla] Drug: Trastuzumab Drug: Docetaxel	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: A Randomized, Multicenter, Phase ii Study of the Efficacy and Safety of Trastuzumab-MCC-DM1 vs. Trastuzumab (Herceptin®) and Docetaxel (Taxotere®) in Patients With Metastatic HER2-positive Breast Cancer Who Have Not Received Prior Chemotherapy for Metastatic Disease

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Progression-free Survival (PFS) by the Investigator Using Modified Response Evaluation Criteria In Solid Tumors (RECIST) [Time Frame: Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)] [Designated as safety issue: No]

  PFS was defined as the time from randomization (R) to first documented investigator-assessed radiographic or clinical disease progression (PD) or death due to any cause, whichever occurred first. For target lesions (TL), PD was defined as at least a 20% increase in the sum of the longest diameter (SLD) of TLs, taking as reference the SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Data for patients without PD or death were censored at the last date of tumor assessment prior to crossover (or, if no tumor assessment was performed after Baseline, at the R date +1 day). Data for patients who were lost to follow-up were censored at the last date of tumor assessment prior to crossover at which the patient was known to be progression free. Data for patients with no post-baseline tumor assessment were censored at the R date +1 day.

Secondary Outcome Measures:

- Overall Survival [Time Frame: Baseline through the data cut-off date of 31 Aug 2011 (up to 2 years, 11 months)] [Designated as safety issue: No]

  Overall survival was defined as the time from randomization to the date of death from any cause. Patients who were alive at the time of analysis were censored at the date on which they were last known to be alive. Patients with no post-baseline were censored at the date of randomization plus 1 day.
- Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [Time Frame: Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 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.
- Duration of Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [Time Frame: Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)] [Designated as safety issue: No]

  Duration of objective response was defined as the time from initial response to investigator-assessed radiographic or clinical disease progression or death on study from any cause. For target lesions, disease progression 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, disease progression 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.
- Clinical Benefit (CB) Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [Time Frame: Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)] [Designated as safety issue: No]

  CB was defined as an objective response (complete response [CR], partial response [PR]) or stable disease (SD) for 6 months after randomization. For target lesions (TL), CR=the disappearance of all TL; PR=at least a 30% decrease in the sum of the longest diameter (LD) of TL, taking as reference the baseline sum LD; SD=neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum LD since the treatment started; PD=at least a 20% increase in the sum of the LD of TL, taking as reference the smallest sum of the LD recorded since the treatment started or the appearance of 1 or more new lesions. For non-TL, CR=the disappearance of all non-TL; PR=the persistence of 1 or more non-TL; SD=the persistence of 1 or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits; PD=the appearance of 1 or more new lesions and/or unequivocal progression of existing non-TL.
- Time to Symptom Progression [Time Frame: Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)] [Designated as safety issue: No]

  Time to symptom progression was defined as the time from randomization to the first documentation of a ≥ 5-point decrease from baseline in the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) subscale score of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. The FACT-B questionnaire is a valid and reliable measure of symptoms associated with breast cancer. The TOI-PFB is a 24-item

subscale generated using 3 subsections (Physical Well-Being [7 items], Functional Well-Being [7 items], and Additional Concerns [10 items]) from the FACT-B questionnaire. Patients responded to each item on a scale of 0-4 (Not at all-Very much). The total score ranged from 0 to 96. A higher score indicates fewer symptoms. A positive change score indicates improvement.

- Serum Concentrations (Area Under the Concentration-time Curve [AUC]) of Trastuzumab Emtansine and Total Trastuzumab [Time Frame: Baseline through Cycle 5 (up to 4 months)] [Designated as safety issue: No]
  Serum samples were collected from all 67 patients enrolled in the trastuzumab emtansine arm using sparse pharmacokinetic sampling. Blood samples were collected prior to dosing and 30 minutes post-infusion of trastuzumab emtansine at Cycles 1 and 5. Serum samples were assayed for trastuzumab emtansine and total trastuzumab (sum of unconjugated trastuzumab and emtansine conjugated to trastuzumab) in indirect sandwich ELISAs. The area under the concentration-time curve (AUC) was estimated based on non-compartmental analysis using WinNonlin (Version 5.2.1) software.
- Plasma Concentration of Free Emtansine [Time Frame: Baseline through Cycle 5 (up to 4 months)] [Designated as safety issue: No]
  Plasma samples were collected from all 67 patients in the trastuzumab emtansine group 30 minutes post-infusion of trastuzumab emtansine at Cycles 1 and 5. The plasma samples were assayed for free emtansine in a mass-spectrometric assay.

Enrollment: 137
Study Start Date: September 2008
Primary Completion Date: November 2010
Study Completion Date: May 2012

Arms	Assigned Interventions
Experimental: Trastuzumab emtansine Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.	Drug: Trastuzumab emtansine [Kadcyla] The total dose depended on the patient's weight on Day 1 of each cycle. Trastuzumab emtansine was administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease (or until second disease progression for patients who crossed over), unacceptable toxicity, or study closure, whichever occurred first. Other Names: trastuzumab-DM1 trastuzumab-MCC-DM1 T-DM1
Active Comparator: Trastuzumab + docetaxel Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.	Drug: Trastuzumab The dose of trastuzumab was recalculated if body weight changed by more than ±10% from baseline. Trastuzumab was administered every 3 weeks until investigator-assessed radiographic or clinical progressive disease, or unmanageable toxicity. Patients in the trastuzumab + docetaxel arm who discontinued study treatment because of progressive disease were eligible to cross-over to trastuzumab emtansine treatment until a second progressive disease event, clinical deterioration, and/or intolerance.

Arms	Assigned Interventions
	Other Names: Herceptin Drug: Docetaxel Docetaxel was given at a dose of 75 or 100 mg/ m^2 based on the investigator's decision. Patients in the trastuzumab + docetaxel arm who discontinued study treatment because of progressive disease were eligible to cross-over to trastuzumab emtansine treatment until a second progressive disease event, clinical deterioration, and/or intolerance. Other Names: Taxotere

Eligibility

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

Criteria

Inclusion Criteria:

- Histologically or cytologically confirmed adenocarcinoma of the breast with locally advanced or metastatic disease, and a candidate for chemotherapy.
- Human epidermal growth factor receptor 2 (HER2)-positive.
- No prior chemotherapy for their metastatic breast cancer (MBC).
- Measurable disease.
- Age ≥ 18 years.
- For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective, non-hormonal form of contraception or 2 effective forms of non-hormonal contraception by the patient and/or partner. Contraception use must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the study.

Exclusion Criteria:

- History of any chemotherapy for MBC.
- An interval of < 6 months from the completion of cytotoxic chemotherapy in the neo-adjuvant or adjuvant setting until the time of metastatic diagnosis.
- Trastuzumab ≤ 21 days prior to randomization.
- Hormone therapy < 7 days prior to randomization.
- Current peripheral neuropathy of Grade ≥ 3.
- History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those previously mentioned.
- Previous radiotherapy for the treatment of unresectable, locally advanced or metastatic breast cancer is not allowed if more than 25% of marrow-bearing bone has been irradiated or the last fraction of radiotherapy has been administered within approximately 3 weeks prior to randomization.

- Brain metastases that are untreated, symptomatic, or require therapy to control symptoms or any radiation, surgery, or other therapy to control symptoms from brain metastases within 2 months prior to randomization.
- History of exposure to the following cumulative doses of anthracyclines: Doxorubicin or liposomal doxorubicin > 500 mg/m^2; epirubicin > 900 mg/m^2; mitoxantrone > 120mg/m^2 and idarubicin > 90 mg/m^2.
- Current unstable angina.
- History of symptomatic congestive heart failure, or ventricular arrhythmia requiring treatment.
- History of myocardial infarction within 6 months prior to randomization.
- Left ventricular ejection fraction (LVEF) below 50% within approximately 28 days prior to randomization.
- History of decreased LVEF or symptomatic congestive heart failure (CHF) with previous adjuvant trastuzumab treatment.
- Cardiac troponin I ≥ 0.2 ng/mL within 28 days of randomization.
- Severe dyspnea at rest because of complications of advanced malignancy or requiring current continuous oxygen therapy.
- Current severe, uncontrolled systemic disease (eg, clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
- Major surgical procedure or significant traumatic injury within approximately 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment.
- Current pregnancy or lactation.
- History of receiving any investigational treatment within approximately 28 days prior to randomization.
- Current known infection with human immunodeficiency virus (HIV), active hepatitis B and/or hepatitis C virus.
- History of intolerance (including Grade 3-4 infusion reaction) or hypersensitivity to trastuzumab, murine proteins, or docetaxel.
- Known hypersensitivity to any of the study drugs, including the excipients, or any drugs formulated in polysorbate 80.
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.

Contacts and Locations

Investigators

Study Director:	Ellie Guardino, MD/PhD	Genentech, Inc.

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	BO21976 TDM4450g [Genentech]
Health Authority:	United States: Food and Drug Administration

Participant Flow

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Overall Study

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
Started	67	70
Completed	14	19
Not Completed	53	51
Disease progression	42	36
Adverse Event	5	6
Subject/guardian decision to discontinue	3	0
Death	1	1
Not specified	1	0
Physician Decision	1	0
Not treated	0	2
Physician/patient decision to withdraw	0	6

Baseline Characteristics

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.

	Description
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Baseline Measures

	Trastuzumab Emtansine	Trastuzumab + Docetaxel	Total
Number of Participants	67	70	137
Age, Continuous [units: years] Mean (Standard Deviation)	54.3 (12.6)	52.1 (10.7)	53.2 (11.7)
Gender, Male/Female [units: participants]			
Female	67	70	137
Male	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival (PFS) by the Investigator Using Modified Response Evaluation Criteria In Solid Tumors (RECIST)
Measure Description	PFS was defined as the time from randomization (R) to first documented investigator-assessed radiographic or clinical disease progression (PD) or death due to any cause, whichever occurred first. For target lesions (TL), PD was defined as at least a 20% increase in the sum of the longest diameter (SLD) of TLs, taking as reference the SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Data for patients without PD or death were censored at the last date of tumor assessment prior to crossover (or, if no tumor assessment was performed after Baseline, at the R date +1 day). Data for patients who were lost to follow-up were censored at the last date of tumor assessment prior to crossover at which the patient was known to be progression free. Data for patients with no post-baseline tumor assessment were censored at the R date +1 day.
Time Frame	Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized patients.

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Measured Values

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
Number of Participants Analyzed	67	70
Progression-free Survival (PFS) by the Investigator Using Modified Response Evaluation Criteria In Solid Tumors (RECIST) [units: Months] Median (95% Confidence Interval)	14.2 (10.6 to NA) [1]	9.2 (8.2 to 11.2)

[1] The upper limit of the 95% confidence interval was not reached because of insufficient events.

2. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival was defined as the time from randomization to the date of death from any cause. Patients who were alive at the time of analysis were censored at the date on which they were last known to be alive. Patients with no post-baseline were censored at the date of randomization plus 1 day.
Time Frame	Baseline through the data cut-off date of 31 Aug 2011 (up to 2 years, 11 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized patients.

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.

	Description
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Measured Values

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
Number of Participants Analyzed	67	70
Overall Survival [units: Months] Median (95% Confidence Interval)	NA (NA to NA) [1]	NA (25.6 to NA) [2]

[1] The median and the upper and lower confidence intervals were not reached because of insufficient events.
[2] The median and the upper confidence intervals were not reached because of insufficient events.

3. Secondary 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 data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)
Safety Issue?	No

Analysis Population Description

All randomized patients with measureable disease at Baseline.

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Measured Values

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
Number of Participants Analyzed	67	69
Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [units: Percentage of patients] Number (90% Confidence Interval)	64.2 (51.8 to 74.8)	58.0 (45.5 to 69.2)

4. 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 investigator-assessed radiographic or clinical disease progression or death on study from any cause. For target lesions, disease progression 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, disease progression 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 data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)
Safety Issue?	No

Analysis Population Description

All randomized patients with measureable disease at Baseline. Only patients with an objective response were included in the analysis.

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Measured Values

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
Number of Participants Analyzed	43	40
Duration of Objective Response Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [units: Months] Median (95% Confidence Interval)	NA (15.0 to NA) [1]	9.5 (6.6 to 10.6)

[1] The median and the upper confidence intervals were not reached because of insufficient events.

5. Secondary Outcome Measure:

Measure Title	Clinical Benefit (CB) Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST)
Measure Description	CB was defined as an objective response (complete response [CR], partial response [PR]) or stable disease (SD) for 6 months after randomization. For target lesions (TL), CR=the disappearance of all TL; PR=at least a 30% decrease in the sum of the longest diameter (LD) of TL, taking as reference the baseline sum LD; SD=neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum LD since the treatment started; PD=at least a 20% increase in the sum of the LD of TL, taking as reference the smallest sum of the LD recorded since the treatment started or the appearance of 1 or more new lesions. For non-TL, CR=the disappearance of all non-TL; PR=the persistence of 1 or more non-TL; SD=the persistence of 1 or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits; PD=the appearance of 1 or more new lesions and/or unequivocal progression of existing non-TL.
Time Frame	Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)
Safety Issue?	No

Analysis Population Description

All randomized patients with measurable disease at Baseline.

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Measured Values

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
Number of Participants Analyzed	67	69
Clinical Benefit (CB) Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) [units: Percentage of patients] Number (90% Confidence Interval)	74.6 (63.2 to 84.2)	81.2 (70.7 to 89.1)

6. Secondary Outcome Measure:

Measure Title	Time to Symptom Progression
Measure Description	Time to symptom progression was defined as the time from randomization to the first documentation of a ≥ 5-point decrease from baseline in the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) subscale score of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. The FACT-B questionnaire is a valid and reliable measure of symptoms associated with breast cancer. The TOI-PFB is a 24-item subscale generated using 3 subsections (Physical Well-Being [7 items], Functional Well-Being [7 items], and Additional Concerns [10 items]) from the FACT-B questionnaire. Patients responded to each item on a scale of 0-4 (Not at all-Very much). The total score ranged from 0 to 96. A higher score indicates fewer symptoms. A positive change score indicates improvement.
Time Frame	Baseline through the data cut-off date of 15 Nov 2010 (up to 2 years, 2 months)
Safety Issue?	No

Analysis Population Description

All randomized patients with a Baseline and at least 1 post-Baseline valid score.

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Measured Values

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
Number of Participants Analyzed	65	67
Time to Symptom Progression	7.5 (4.2 to 15.1)	3.5 (2.1 to 6.5)

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
[units: Months] Median (95% Confidence Interval)		

7. Secondary Outcome Measure:

Measure Title	Serum Concentrations (Area Under the Concentration-time Curve [AUC]) of Trastuzumab Emtansine and Total Trastuzumab
Measure Description	Serum samples were collected from all 67 patients enrolled in the trastuzumab emtansine arm using sparse pharmacokinetic sampling. Blood samples were collected prior to dosing and 30 minutes post-infusion of trastuzumab emtansine at Cycles 1 and 5. Serum samples were assayed for trastuzumab emtansine and total trastuzumab (sum of unconjugated trastuzumab and emtansine conjugated to trastuzumab) in indirect sandwich ELISAs. The area under the concentration-time curve (AUC) was estimated based on non-compartmental analysis using WinNonlin (Version 5.2.1) software.
Time Frame	Baseline through Cycle 5 (up to 4 months)
Safety Issue?	No

Analysis Population Description

Pharmacokinetic evaluable population: Patients who had adequate concentration-time data to estimate at least 1 pharmacokinetic parameter.

Reporting Groups

	Description
Trastuzumab Emtansine 3.6 mg/kg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.

Measured Values

	Trastuzumab Emtansine 3.6 mg/kg
Number of Participants Analyzed	67
Serum Concentrations (Area Under the Concentration-time Curve [AUC]) of Trastuzumab Emtansine and Total Trastuzumab [units: day•µg/mL] Mean (Standard Deviation)	
Trastuzumab emtansine Cycle 1 (n=62)	495 (158)
Trastuzumab emtansine Cycle 5 (n=39)	473 (141)
Total trastuzumab Cycle 1 (n=60)	700 (260)

	Trastuzumab Emtansine 3.6 mg/kg
Total trastuzumab Cycle 5 (n=38)	788 (323)

8. Secondary Outcome Measure:

Measure Title	Plasma Concentration of Free Emtansine
Measure Description	Plasma samples were collected from all 67 patients in the trastuzumab emtansine group 30 minutes post-infusion of trastuzumab emtansine at Cycles 1 and 5. The plasma samples were assayed for free emtansine in a mass-spectrometric assay.
Time Frame	Baseline through Cycle 5 (up to 4 months)
Safety Issue?	No

Analysis Population Description

Pharmacokinetic evaluable population: Patients who had adequate concentration-time data to estimate at least 1 pharmacokinetic parameter.

Reporting Groups

	Description
Trastuzumab Emtansine 3.6 mg/kg	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.

Measured Values

	Trastuzumab Emtansine 3.6 mg/kg
Number of Participants Analyzed	67
Plasma Concentration of Free Emtansine [units: ng/mL] Mean (Standard Deviation)	
Cycle 1 (n=62)	5.11 (2.34)
Cycle 5 (n=39)	4.71 (2.25)

Reported Adverse Events

Time Frame	Adverse events were collected from randomization until 30 days following the last treatment, until the early termination visit, or until treatment-related adverse events resolved or stabilized, whichever occurred first.
Additional Description	Safety population: All randomized patients who received at least 1 dose of study treatment. In the trastuzumab + docetaxel (T+D) group, 2 patients received no treatment and 2 patients received a dose of trastuzumab emtansine (TE) and were included in that group for safety analyses, resulting in 66 patients in the T+D group and 69 in the TE group.

Reporting Groups

	Description
Trastuzumab Emtansine	Patients received trastuzumab emtansine 3.6 mg/kg intravenously (IV) administered over 30-90 minutes every 3 weeks on Day 1 of each 21-day cycle.
Trastuzumab + Docetaxel	Patients received a loading dose of trastuzumab 8 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of Cycle 1 followed by trastuzumab 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV on Day 1 of all subsequent 21-day cycles.

Serious Adverse Events

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Total	14/69 (20.29%)	17/66 (25.76%)
Blood and lymphatic system disorders		
Anaemia †	0/69 (0%)	1/66 (1.52%)
Febrile neutropenia †	0/69 (0%)	6/66 (9.09%)
Cardiac disorders		
Atrial fibrillation †	1/69 (1.45%)	1/66 (1.52%)
Cardiopulmonary failure †	0/69 (0%)	1/66 (1.52%)
Supraventricular extrasystoles †	1/69 (1.45%)	0/66 (0%)
Gastrointestinal disorders		
Abdominal pain †	1/69 (1.45%)	0/66 (0%)
Intestinal obstruction †	0/69 (0%)	1/66 (1.52%)
Vomiting †	1/69 (1.45%)	0/66 (0%)
General disorders		

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Chills †	1/69 (1.45%)	0/66 (0%)
Oedema peripheral †	0/69 (0%)	1/66 (1.52%)
Pyrexia †	1/69 (1.45%)	0/66 (0%)
Sudden death †	1/69 (1.45%)	0/66 (0%)
Immune system disorders		
Hypersensitivity †	0/69 (0%)	1/66 (1.52%)
Infections and infestations		
Arthritis infective †	0/69 (0%)	1/66 (1.52%)
Cellulitis †	0/69 (0%)	2/66 (3.03%)
Pneumonia †	5/69 (7.25%)	0/66 (0%)
Sepsis †	1/69 (1.45%)	0/66 (0%)
Injury, poisoning and procedural complications		
Spinal compression fracture †	0/69 (0%)	1/66 (1.52%)
Investigations		
C−reactive protein increased †	0/69 (0%)	1/66 (1.52%)
Metabolism and nutrition disorders		
Dehydration †	1/69 (1.45%)	0/66 (0%)
Hypercalcaemia †	1/69 (1.45%)	0/66 (0%)
Hyperglycaemia †	0/69 (0%)	1/66 (1.52%)
Metabolic acidosis †	0/69 (0%)	1/66 (1.52%)
Tumour lysis syndrome †	1/69 (1.45%)	0/66 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Breast cancer †	0/69 (0%)	1/66 (1.52%)
Renal and urinary disorders		
Renal failure acute †	0/69 (0%)	1/66 (1.52%)
Respiratory, thoracic and mediastinal disorders		

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Alveolitis allergic †	0/69 (0%)	1/66 (1.52%)
Dyspnoea †	0/69 (0%)	1/66 (1.52%)
Epistaxis †	0/69 (0%)	1/66 (1.52%)
Pleural effusion †	1/69 (1.45%)	1/66 (1.52%)
Pleuritic pain †	1/69 (1.45%)	0/66 (0%)
Pneumonitis †	1/69 (1.45%)	0/66 (0%)
Pulmonary embolism †	0/69 (0%)	1/66 (1.52%)
Vascular disorders		
Deep vein thrombosis †	0/69 (0%)	1/66 (1.52%)
Hypertensive crisis †	1/69 (1.45%)	0/66 (0%)
Hypovolaemic shock †	1/69 (1.45%)	0/66 (0%)

† Indicates events were collected by systematic assessment.

Other Adverse Events

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

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Total	66/69 (95.65%)	66/66 (100%)
Blood and lymphatic system disorders		
Anaemia †	9/69 (13.04%)	18/66 (27.27%)
Leukopenia †	7/69 (10.14%)	17/66 (25.76%)
Neutropenia †	11/69 (15.94%)	43/66 (65.15%)
Thrombocytopenia †	19/69 (27.54%)	4/66 (6.06%)
Cardiac disorders		
Palpitations †	4/69 (5.8%)	2/66 (3.03%)
Eye disorders		
Conjunctivitis †	5/69 (7.25%)	3/66 (4.55%)

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Dry eye †	6/69 (8.7%)	0/66 (0%)
Lacrimation increased †	5/69 (7.25%)	13/66 (19.7%)
Gastrointestinal disorders		
Abdominal pain †	6/69 (8.7%)	4/66 (6.06%)
Abdominal pain upper †	12/69 (17.39%)	4/66 (6.06%)
Constipation †	16/69 (23.19%)	15/66 (22.73%)
Diarrhoea †	11/69 (15.94%)	30/66 (45.45%)
Dry mouth †	11/69 (15.94%)	3/66 (4.55%)
Dyspepsia †	11/69 (15.94%)	8/66 (12.12%)
Gingival bleeding †	4/69 (5.8%)	0/66 (0%)
Nausea †	34/69 (49.28%)	29/66 (43.94%)
Oral pain †	0/69 (0%)	4/66 (6.06%)
Stomatitis †	8/69 (11.59%)	13/66 (19.7%)
Toothache †	2/69 (2.9%)	7/66 (10.61%)
Vomiting †	17/69 (24.64%)	17/66 (25.76%)
General disorders		
Asthenia †	16/69 (23.19%)	14/66 (21.21%)
Chest pain †	6/69 (8.7%)	4/66 (6.06%)
Chills †	10/69 (14.49%)	5/66 (7.58%)
Fatigue †	34/69 (49.28%)	30/66 (45.45%)
Influenza like illness †	5/69 (7.25%)	1/66 (1.52%)
Mucosal inflammation †	4/69 (5.8%)	12/66 (18.18%)
Oedema peripheral †	7/69 (10.14%)	28/66 (42.42%)
Pain †	2/69 (2.9%)	5/66 (7.58%)
Pyrexia †	28/69 (40.58%)	15/66 (22.73%)
Infections and infestations		

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Bronchitis †	1/69 (1.45%)	5/66 (7.58%)
Influenza †	5/69 (7.25%)	2/66 (3.03%)
Nasopharyngitis †	11/69 (15.94%)	10/66 (15.15%)
Pharyngitis †	4/69 (5.8%)	3/66 (4.55%)
Rhinitis †	5/69 (7.25%)	1/66 (1.52%)
Sinusitis †	7/69 (10.14%)	5/66 (7.58%)
Upper respiratory tract infection †	10/69 (14.49%)	8/66 (12.12%)
Urinary tract infection †	5/69 (7.25%)	11/66 (16.67%)
Injury, poisoning and procedural complications		
Contusion †	4/69 (5.8%)	1/66 (1.52%)
Infusion related reaction †	8/69 (11.59%)	4/66 (6.06%)
Investigations		
Alanine aminotransferase increased †	18/69 (26.09%)	4/66 (6.06%)
Aspartate aminotransferase increased †	30/69 (43.48%)	4/66 (6.06%)
Blood alkaline phosphatase increased †	10/69 (14.49%)	2/66 (3.03%)
Blood lactate dehydrogenase increased †	6/69 (8.7%)	1/66 (1.52%)
Gamma−glutamyltransferase increased †	4/69 (5.8%)	0/66 (0%)
Platelet count decreased †	4/69 (5.8%)	0/66 (0%)
Weight increased †	0/69 (0%)	4/66 (6.06%)
Metabolism and nutrition disorders		
Decreased appetite †	13/69 (18.84%)	11/66 (16.67%)
Hypokalaemia †	12/69 (17.39%)	6/66 (9.09%)
Musculoskeletal and connective tissue disorders		
Arthralgia †	16/69 (23.19%)	20/66 (30.3%)
Back pain †	19/69 (27.54%)	21/66 (31.82%)
Bone pain †	5/69 (7.25%)	15/66 (22.73%)

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Muscle spasms †	4/69 (5.8%)	6/66 (9.09%)
Musculoskeletal chest pain †	4/69 (5.8%)	3/66 (4.55%)
Musculoskeletal pain †	9/69 (13.04%)	4/66 (6.06%)
Myalgia †	7/69 (10.14%)	12/66 (18.18%)
Neck pain †	5/69 (7.25%)	2/66 (3.03%)
Pain in extremity †	9/69 (13.04%)	15/66 (22.73%)
Nervous system disorders		
Dizziness †	3/69 (4.35%)	6/66 (9.09%)
Dysgeusia †	6/69 (8.7%)	15/66 (22.73%)
Headache †	28/69 (40.58%)	12/66 (18.18%)
Hypoaesthesia †	4/69 (5.8%)	3/66 (4.55%)
Neuropathy peripheral †	10/69 (14.49%)	10/66 (15.15%)
Paraesthesia †	6/69 (8.7%)	11/66 (16.67%)
Peripheral sensory neuropathy †	5/69 (7.25%)	14/66 (21.21%)
Psychiatric disorders		
Anxiety †	6/69 (8.7%)	5/66 (7.58%)
Depression †	5/69 (7.25%)	4/66 (6.06%)
Insomnia †	8/69 (11.59%)	12/66 (18.18%)
Renal and urinary disorders		
Dysuria †	1/69 (1.45%)	4/66 (6.06%)
Reproductive system and breast disorders		
Breast pain †	1/69 (1.45%)	8/66 (12.12%)
Respiratory, thoracic and mediastinal disorders		
Cough †	18/69 (26.09%)	14/66 (21.21%)
Dyspnoea †	10/69 (14.49%)	18/66 (27.27%)
Dyspnoea exertional †	1/69 (1.45%)	6/66 (9.09%)

	Trastuzumab Emtansine	Trastuzumab + Docetaxel
	Affected/At Risk (%)	Affected/At Risk (%)
Epistaxis †	19/69 (27.54%)	5/66 (7.58%)
Oropharyngeal pain †	8/69 (11.59%)	8/66 (12.12%)
Rhinorrhoea †	5/69 (7.25%)	4/66 (6.06%)
Skin and subcutaneous tissue disorders		
Acne †	6/69 (8.7%)	0/66 (0%)
Alopecia †	3/69 (4.35%)	44/66 (66.67%)
Dermatitis †	1/69 (1.45%)	4/66 (6.06%)
Dry skin †	4/69 (5.8%)	2/66 (3.03%)
Erythema †	2/69 (2.9%)	5/66 (7.58%)
Nail discolouration †	0/69 (0%)	4/66 (6.06%)
Nail disorder †	7/69 (10.14%)	16/66 (24.24%)
Palmar−plantar erythrodysaesthesia syndrome †	2/69 (2.9%)	4/66 (6.06%)
Pruritus †	2/69 (2.9%)	8/66 (12.12%)
Rash †	12/69 (17.39%)	15/66 (22.73%)
Vascular disorders		
Flushing †	2/69 (2.9%)	4/66 (6.06%)
Hot flush †	0/69 (0%)	10/66 (15.15%)
Hypertension †	9/69 (13.04%)	6/66 (9.09%)
Lymphoedema †	3/69 (4.35%)	5/66 (7.58%)

† Indicates events were collected by systematic assessment.

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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