The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

A Phase 2 Randomized Study of Trastuzumab Emtansine (T-DM1) versus Trastuzumab + Docetaxel in Patients With HER2-Positive Metastatic Breast Cancer

Hurvitz, et al

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REDACTED PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, PHASE II STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE (T-DM1) VS. TRASTUZUMAB (HERCEPTIN) AND DOCETAXEL (TAXOTERE) IN PATIENTS WITH METASTATIC HER2-POSITIVE BREAST CANCER WHO HAVE NOT RECEIVED PRIOR CHEMOTHERAPY FOR METASTATIC DISEASE**
PROTOCOL NUMBER:	TDM4450g
STUDY DRUG:	Trastuzumab emtansine (T-DM1)
IND:	71,072
SPONSORS:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A. F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 Basel, Switzerland

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1. MATERIALS AND METHODS

1.1 PATIENTS

1.1.1 PATIENT SELECTION

This study will enroll patients with HER2-positive, unresectable, locally advanced breast cancer and/or metastatic breast cancer who have not received prior chemotherapy for their metastatic disease.

1.1.2 INCLUSION CRITERIA

Patients must meet the following inclusion criteria to be eligible for study entry:

a. Disease-Specific Criteria

- Histologically or cytologically confirmed adenocarcinoma of the breast with locally advanced or metastatic disease, and a candidate for chemotherapy
    - Patients with locally advanced disease must have recurrent or progressive disease after failing initial attempts at local control. The disease must be considered to be unresectable
- HER2-positive (immunohistochemistry [IHC] 3+ or fluorescence in situ hybridization [FISH]-positive) based on local laboratory assay results
- No prior chemotherapy for their MBC (hormonal therapy is allowed)
- Measurable disease per modified Response Evaluation Criteria in Solid Tumors (RECIST)
    - Patients should have at least one target lesion ≥ 2 cm on conventional CT scan or ≥ 1cm on a spiral CT scan

- Tumor blocks or 11 unstained slides available for confirmatory central laboratory HER2 testing

b. General Criteria

- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function, evidenced by the following laboratory results within approximately 21 days prior to randomization:
    - Absolute neutrophil count > 1500 cells/mm3
    - Platelet count > 100,000 cells/mm3
    - Hemoglobin > 9.0 g/dL; patients are allowed to be transfused with red blood cells to obtain this level
    - Total bilirubin ≤ 1.5 × the upper limit of normal (ULN)
    - SGOT (AST), SGPT (ALT), and alkaline phosphatase ≤ 2.5 × ULN, with the following exception: patients with bone metastases: alkaline phosphatase ≤ 5 × ULN
    - Serum creatinine < 1.5 × ULN
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) < 1.5 × ULN (unless on therapeutic anticoagulation or due to a lupus anticoagulant)
- For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective, non-hormonal form of contraception or two 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
- Specific country requirements will be followed (e.g., in the United Kingdom, women of childbearing potential and male subjects and their partners of childbearing potential must use two methods of

contraception [one of which must be a barrier method] for the duration of the study)

1.1.3. EXCLUSION CRITERIA

a. Cancer-Related Criteria

- History of any chemotherapy for MBC; prior hormonal therapy is allowed
- An interval of < 6 months from the completion of cytotoxic chemotherapy (excluding hormonal therapy) 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 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0
- 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
    - 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
    - CT or magnetic resonance imaging (MRI) scan of the brain is mandatory (within approximately 28 days prior to randomization) in cases of clinical suspicion of brain metastases or in a patient with any prior history of brain metastases

- History of exposure to the following cumulative doses of anthracyclines:
    - Doxorubicin or liposomal doxorubicin > 500 mg/m^2
    - Epirubicin > 900 mg/m^2
    - Mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2
    - If another anthracycline or more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 of doxorubicin

b. Cardiopulmonary Function

- Current unstable angina
- History of symptomatic congestive heart failure (CHF; New York Heart Association [NYHA] classes II−IV), or ventricular arrhythmia that requires 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 a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment
- Cardiac troponin I ≥ 0.2 ng/mL within approximately 28 days prior to randomization
- Severe dyspnea at rest because of complications of advanced malignancy or requiring current continuous oxygen therapy

c. General Criteria

- Current severe, uncontrolled systemic disease (e.g., 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 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

II. SCHEMA AND TREATMENT PLAN, INCLUDING ADMINISTRATION SCHEDULE

2. STUDY DESIGN

2.1 DESCRIPTION OF THE STUDY

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

A total of 120 patients will be enrolled from approximately 100 sites worldwide. Following the determination of eligibility, patients will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: T-DM1 3.6 mg/kg intravenous (IV) over 30−90 minutes on Day 1 every 3 weeks
- Arm B: For Cycle 1, on Day 1, trastuzumab 8 mg/kg IV + docetaxel either 75 mg/m^2 or 100 mg/m^2 IV. For subsequent cycles, trastuzumab 6 mg/kg IV on Day 1 every 3 weeks + docetaxel 75−100 mg/m^2 IV every 3 weeks

A hierarchical dynamic randomization scheme will be used to ensure an approximately equal sample size for the two treatment arms 1) overall and 2) within each of the eight categories defined by world region (U.S., ex−U.S.) and by the following two prognostic factors: prior adjuvant trastuzumab therapy (yes, no) and disease-free interval (DFI; ≤ 24 months or > 24 months).

All patients will have histologically or cytologically confirmed HER2-overexpressing adenocarcinoma of the breast. The patient's HER2 status will be

considered positive if the local institution or reference lab reported Grade 3+ staining intensity (on a scale of 0 to 3) by means of IHC or FISH+ and will be retrospectively confirmed by IHC and/or FISH in a central laboratory using archival paraffin-embedded tumor tissue. Patients must have metastatic disease and/or locally recurrent disease not amenable to resection with curative intent. Patients with locally advanced disease include patients with recurrent or progressive disease after receiving primary therapy (per modified RECIST). Patients must have measurable disease.

Tumor assessments will be conducted every 9 weeks from the start of treatment until documented progressive disease (PD) or death on study, regardless of dose delays or interruptions or both. Patient management decisions will be made based on tumor assessments performed by investigators.

In Treatment Arm A, patients who have not yet progressed but who have become intolerant to T-DM1 (i.e., experience unacceptable toxicity that requires discontinuation from T-DM1) and for whom single-agent trastuzumab is an option will be eligible to remain on the study and to receive trastuzumab administered according to prescribing guidelines in the metastatic setting until the first disease progression, clinical deterioration, and/or unacceptable toxicity. T-DM1 must be permanently discontinued and will not be allowed to be restarted. The decision to change treatment from T-DM1 to trastuzumab must be approved by the Medical Monitor in accordance with standard practice guidelines.

In Treatment Arm B, patients who have not yet progressed but who have become intolerant to either docetaxel or trastuzumab (i.e., experience unacceptable toxicity that requires discontinuation from docetaxel or trastuzumab) may remain in the study and to receive single-agent trastuzumab or docetaxel, respectively, until disease progression, clinical deterioration, or intolerance.

Patients on Treatment Arm B who discontinue study treatment because of disease progression may be eligible to cross over to T-DM1 treatment, starting at 3.6 mg/kg, until a second disease progression event, clinical deterioration, and/or intolerance.

The decision to cross over from the control arm to T-DM1 must be approved by the Medical Monitor. Disease progression must be documented with the Medical Monitor. Additionally, the Medical Monitor must approve that it is safe for the patient to continue on study treatment with T-DM1, i.e., there are no significant and/or related ongoing adverse events and/or a change in the patient's clinical status that would put the patient's safety at risk.

Patients who are discontinued from study treatment for reasons other than disease progression will be followed with tumor assessments every 9 weeks until disease progression. Subsequently, all patients will be followed for survival and subsequent anti-cancer therapies approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.

Patients may remain on study treatment until disease progression, unmanageable toxicity, or study termination by the Sponsor. The study will be terminated at approximately the time of last patient in (LPI) plus 2 years. The primary analysis will be performed when approximately 72 investigator-assessed progression-free survival (PFS) events have occurred, which is expected to occur approximately 12 months from the completion of enrollment. Further analyses may be performed at study closure.

An extension study is planned to be available for patients who were randomized to receive T-DM1 (and/or patients who crossover to T-DM1) who continue to receive benefit from T-DM1 after the final analysis for PFS. At that time, any patient receiving T-DM1 who is deriving clinical benefit will be transitioned to the extension study.

2.2 DOSAGE AND ADMINISTRATION

2.2.1 T-DM1

T-DM1 will be given at a dose of 3.6 mg/kg IV every 3 weeks until disease progression (second disease progression for patients who cross over), unacceptable toxicity, or study closure, whichever occurs first. The total dose will depend on the patient's weight on Day 1 of each cycle.

T-DM1 will be administered in 21-day cycles. A dose delay of up to 21 days is allowed as described below if needed for resolution of drug-related toxicities.) If the timing of a protocol-mandated procedure (such as the infusion of T-DM1) coincides with a holiday that precludes the procedure, the procedure should be performed on the nearest following date, with subsequent protocol-specified procedures rescheduled accordingly.

The initial dose will be administered over 90 minutes (± 10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be observed for at least 90 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of T-DM1 may be administered over 30 minutes (± 10 minutes), with a minimum 30-minute observation period post-infusion. Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable. Vital signs should be recorded immediately before, every 15 minutes during, and 90 minutes after the first T-DM1 infusion. In subsequent cycles, vital signs should be recorded pre- and post-infusion.

2.2.2 TRASTUZUMAB

Trastuzumab will be administered at a dose of 8 mg/kg IV on Cycle 1 Day 1 followed by 6 mg/kg IV every 3 weeks. Docetaxel will be administered at a dose of 75 mg/m^2 or 100 mg/m^2 IV. Treatment may be continued until disease progression, unacceptable toxicity, or study closure. If docetaxel is discontinued early, trastuzumab may be continued every 3 weeks. Similarly, if trastuzumab is discontinued early, docetaxel may be continued every 3 weeks.

If a patient misses a dose of trastuzumab by more than 1 week, a re-loading dose of trastuzumab (8 mg/kg) may be given in the same fashion as for Cycle 1. In general, subsequent maintenance doses of trastuzumab of 6 mg/kg will be given every 3 weeks starting 3 weeks later.

2.2.3 DOCETAXEL

Refer to the Taxotere Package Insert/national prescribing information for information on formulation, preparation, and administration. Premedication is required according to standard practice guidelines.

Institutions should follow their administration guidelines for docetaxel, including anti-emetics and corticosteroid premedication prior to docetaxel infusions. Note that all patients should receive corticosteroid premedication in order to reduce the incidence and severity of hypersensitivity reactions and fluid retention.

In the event of extravasation and/or a suspected anaphylactic reaction during the docetaxel infusion, institutional guidelines for the treatment of docetaxel extravasation and for the treatment of anaphylaxis should be followed.

Docetaxel will be given at a dose of 75 mg/m^2 or 100 mg/m^2 on Day 1 every 3 weeks based on the investigator's decision.

III. RULES FOR DOSE MODIFICATION

3. DOSAGE MODIFICATION

3.1 T-DM1

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values are acceptable. In general, it is recommended that all T-DM1−related toxicities have resolved to Grade ≤ 1 or baseline. Protocol requirements for specific toxicities are outlined below.

3.1.1 INFUSION REACTIONS

Infusion of study treatment should be interrupted for patients who develop dyspnea or clinically significant hypotension. Patients who experience a Grade 3 or 4 infusion reaction, acute respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from study treatment.

The infusion should be slowed to ≤ 50% or interrupted for patients who experience any infusion-related symptoms not specified above. When the patient's symptoms have completely resolved, the infusion may be continued at ≤ 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes, if well tolerated. Infusions may be restarted at the full rate during the next cycle, with monitoring as described above.

3.1.2 HEMATOLOGIC TOXICITY

Patients who experience a first Grade 4 thrombocytopenia event may, after adequate recovery to a platelet count of Grade ≤ 1, continue treatment with T-DM1 at a dose of 3.0 mg/kg in subsequent treatment cycles. Patients who experience a second Grade 4 thrombocytopenia event may, after adequate

recovery as defined above, continue treatment with T-DM1 at a dose of 2.4 mg/kg in subsequent treatment cycles. Patients who experience a Grade 4 thrombocytopenia event at the 2.4 mg/kg dose level will be discontinued from study treatment. Patients who experience an adverse event may be checked weekly for a total of 21 days from their last scheduled dose for recovery of platelet counts. If a patient's platelet counts do not recover to baseline or Grade ≤ 1 within the 21 days, the patient will be discontinued. No re-escalation of the T-DM1 dose will be allowed.

3.1.3 HEPATOTOXICITY

Patients receiving T-DM1 who experience a first Grade ≥ 3 transaminase elevation and/or a first Grade ≥ 2 total bilirubin elevation may, after adequate recovery to Grade ≤ 2 (transaminase levels) and/or Grade ≤ 1 (total bilirubin level) or baseline, continue treatment with T-DM1 at a dose of 3.0 mg/kg in subsequent treatment cycles. Patients who experience a second Grade ≥ 3 transaminase elevation and/or a second Grade ≥ 2 total bilirubin elevation may, after adequate recovery as defined above, continue treatment with T-DM1 at a dose of 2.4 mg/kg in subsequent treatment cycles. Patients who experience a Grade ≥ 3 transaminase elevation and/or a Grade ≥ 2 total bilirubin elevation at the 2.4 mg/kg dose level will be discontinued from study treatment. A dose delay of up to 21 days from the patient's last scheduled (but missed) dose is permitted. Patients who experience a Grade ≥ 3 elevation of liver function may be checked weekly for the recovery of transaminases and/or total bilirubin for a total of 21 days from their last scheduled dose. If a patient's transaminases and/or total bilirubin do not recover to baseline or Grade ≤ 1 within the allowable dose delay of 21 days from the patient's last scheduled (but missed) dose, the patient will be discontinued from study treatment. No re-escalation of the T-DM1 dose will be allowed. If a patient experiences an elevated total bilirubin, please check a direct bilirubin.

3.1.4 NEUROTOXICITY

Patients who experience unrecoverable Grade ≥ 3 peripheral neuropathy (i.e., no recovery to Grade ≤ 2 within 21 days of their last dose) will be discontinued from the study.

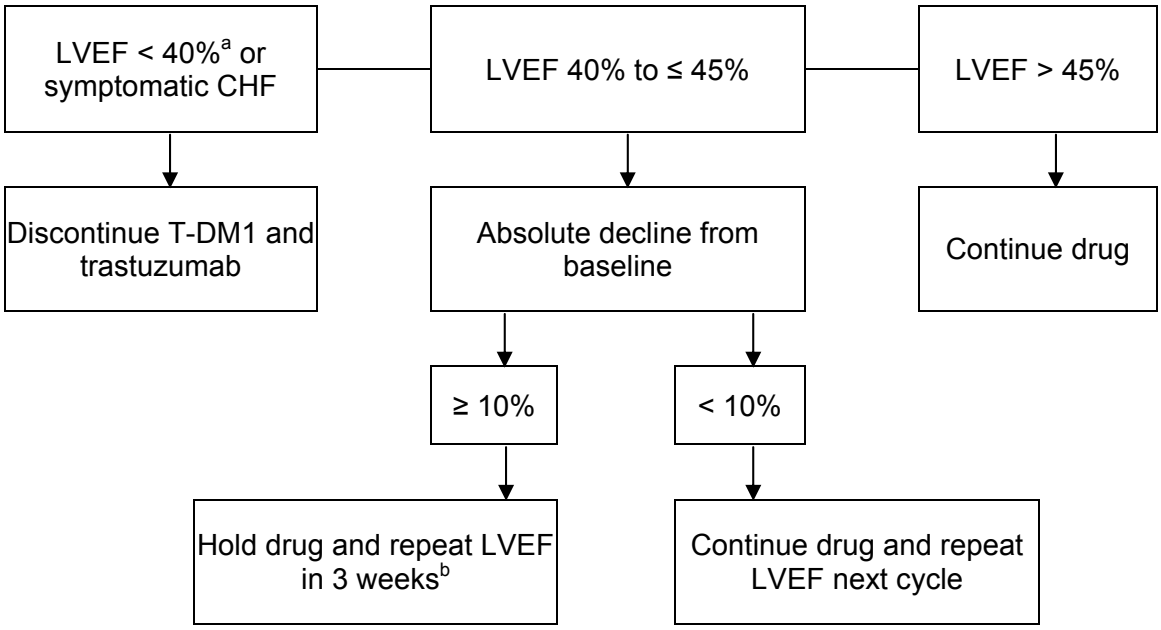
3.1.5 CARDIOTOXICITY

Patients must have a baseline LVEF ≥ 50%. LVEF will be monitored regularly according to the schedule of assessments. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. T-DM1 or trastuzumab will be discontinued in any patient who develops CHF (i.e., Grade ≥ 3 left ventricular systolic dysfunction as defined according to the NCI CTCAE, Version 3.0). CHF should be treated and monitored according to standard medical practice.

T-DM1 or trastuzumab must also be discontinued in all patients, for whom a drop of LVEF to < 40% is documented and confirmed with a repeat assessment within 3 weeks. During this 3-week interval, T-DM1 should be withheld. For patients whose LVEF declines to values between 40% and 45%, the decision to stop or continue T-DM1 or trastuzumab is based on the algorithm shown in Figure 1.

Figure 1

Algorithm for Continuation and Discontinuation of T-DM1 or Trastuzumab Based on LVEF Assessments in Patients



T-DM1 = trastuzumab-MCC-DM1; LVEF = left ventricular ejection fraction; CHF = congestive heart failure.
Note: LVEF assessment results must be available before or on the day of the next scheduled T-DM1 or trastuzumab infusion.
[a]LVEF < 40% can be repeated within 3 weeks, and T-DM1 or trastuzumab should be discontinued if LVEF < 40% is confirmed. T-DM1 or trastuzumab should be held while the repeat LVEF is obtained.
[b]After a second consecutive confirmatory result, discontinue drug.

Trastuzumab or T-DM1 should be held with a decline in LVEF of ≥ 10% points for patients whose LVEF falls to ≤ 45%. For these patients, the LVEF should be repeated in 3 weeks, and the T-DM1 or trastuzumab should be discontinued if the LVEF has not recovered to within 10% points of baseline. The patient should be discontinued if clinically significant cardiac dysfunction or cardiac failure develops or persists.

Decisions regarding continuing treatment with T-DM1 in patients deriving clinical benefit from T-DM1 who experience an asymptomatic decline in left ventricular function must involve the Medical Monitor.

3.1.6 SCHEDULE MODIFICATION

Patients in whom other significant T-DM1–related toxicities have not recovered to Grade ≤ 1 or baseline grade after 21 days from their last scheduled dose may have their dose of T-DM1 delayed for up to 21 days. “Significant” and “related” will be based on the judgment of the investigator (in consultation with the Medical Monitor when appropriate). For example, alopecia even if considered related would most likely not be considered to be significant. Fatigue may not be considered either related or significant.

When these toxicities have reversed to Grade ≤ 1 or baseline, the patient may resume T-DM1 if the delay has not exceeded 21 days. Patients should be re-evaluated weekly during their delay, whenever possible. If re-treatment criteria are met, they may receive T-DM1 either at the previous dose level or at one dose level lower (see Table 1) at the discretion of the investigator.

If patients require a dose reduction, patients will be de-escalated one dose level until they are off of the study. No dose re-escalation will be allowed.

Table 1

Dose-Reduction for T-DM1

Dose Level	Dose
0	3.6 mg/kg
−1	3.0 mg/kg
−2	2.4 mg/kg
−3	Off study

If toxicities do not resolve within the allowable dose delays, the patient will be discontinued from study treatment and will be followed for safety outcomes as described.

3.1.7 OPTIONAL T-DM1 CROSSOVER TREATMENT

Patients on Treatment Arm B who discontinue study treatment because of disease progression may be eligible to cross over to T-DM1 treatment, starting at 3.6 mg/kg, until a second disease progression event, clinical deterioration, and/or intolerance.

The decision to cross over from the control arm to T-DM1 must be approved by the Medical Monitor. Disease progression must be documented with the Medical Monitor. Additionally, the Medical Monitor must approve that it is safe for the patient to continue on study treatment with T-DM1, i.e., there are no significant and/or related ongoing adverse events and/or a change in the patient's clinical status that would put the patient's safety at risk. In general, the safety monitoring of the patient, and the dosing decisions, including dose modifications, should be as described for T-DM1 above.

3.2 TRASTUZUMAB

No dose reduction of trastuzumab is allowed in this study. Administration may be delayed to assess or treat adverse events such as cardiac adverse events or myelosuppression.

3.3 DOCETAXEL

Docetaxel may be delayed due to toxicities. If docetaxel is delayed for more than 3 weeks without recovery, docetaxel should be dose-reduced according to Table 2. If docetaxel is discontinued prior to disease progression, the patient may continue on single-agent trastuzumab.

Docetaxel dose reduction should occur for myelosuppression, hepatic dysfunction, severe peripheral neuropathy, and other toxicities as outlined in

Table 2. Baseline body weight will be used to calculate required doses, and no subsequent dose modifications are required for weight changes for docetaxel.

Table 2
Dose Reduction for Docetaxel

Docetaxel Dose	When
75 or 100 mg/m^2	Starting dose
First 25% reduction (to 55 mg/m^2 if the starting dose was 75 mg/m^2 or 75 mg/m2 if the starting dose was 100 mg/m^2)	• Febrile neutropenia or neutrophils < 500 cells/mm^3 for > 1 week • Platelet count < 75,000 cells/mm^3 (after recovering to a platelet count ≥ 100,000 cells/mm^3) • Severe or cumulative cutaneous reactions
Second 25% dose reduction (to 55 mg/m^2) for patients receiving 75 mg/m^2 (i.e., patients who first developed toxicity while receiving a 100 mg/m^2 dose)	• Febrile neutropenia or neutrophils < 500 cells/mm^3 for > 1 week • Platelet count < 75,000 cells/mm^3 (after recovering to a platelet count ≥ 100,000 cells/mm^3) • Severe or cumulative cutaneous reactions
Permanently discontinue docetaxel	• Severe hypersensitivity reactions • Peripheral neuropathy Grade ≥ 3 without recovery • Severe or cumulative cutaneous reactions at 55 mg/m^2 • Febrile neutropenia or neutrophils < 500 cells/mm^3 for more than 1 week at 55 mg/m^2 • Total bilirubin > ULN without recovery • Serum transaminase (AST/ALT) levels > 1.5 × ULN concurrent with serum alkaline phosphatase levels > 2.5 × ULN without recovery

ULN = upper limit of normal.
Source: See Taxotere (Docetaxel) Prescribing Information and Salminen et al. 1999.

IV. MEASUREMENT OF TREATMENT EFFECT INCLUDING RESPONSE CRITERIA, DEFINITION OF RESPONSE AND SURVIVAL, AND METHODS OF MEASUREMENT

4. OUTCOME MEASURES

4.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint for this study is PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator tumor assessments using modified RECIST, or death on study from any cause. Death on study is defined as death from any cause within 30 days of the last dose of study drug prior to crossover. The first documented PD event prior to crossover in the control arm will be included in the analysis of the primary endpoint of PFS.

4.2 SECONDARY ENDPOINTS

The secondary endpoints for this study are as follows:

- Duration of overall survival, defined as the time from randomization until death from any cause
    - In addition, the survival rate at 12 months will be provided
- Objective response (partial response [PR] plus complete response [CR]) as determined by investigator review of tumor assessments using modified RECIST
    - Objective responses must be confirmed at least 28 days after the initial documentation of response
- Duration of objective response, defined as the first occurrence of a documented objective response until the time of disease progression, as

determined by investigator review of tumor assessments using modified RECIST, or death on study from any cause

- Clinical benefit rate, defined as the proportion of patients who continue to have an objective response (CR or PR) or stable disease for ≥ 6 months from randomization, as determined by investigator review of tumor assessments using modified RECIST
- Pharmacokinetics (PK) properties: serum concentrations of total trastuzumab and T-DM1 and plasma concentrations of free DM1
- Time to symptom progression, defined as the time from randomization to the first documentation of a ≥ 5-point decrease from baseline in the scoring of responses to the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) subscale of the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire (Brady et al. 1997)
    - To measure patient's assessment of pain intensity within the previous 24 hours, a question using a numeric rating scale will be completed (Dworkin et al. 2005), with a Visual Analog Scale (VAS) hashed line

4.3 SAFETY ENDPOINTS

Safety will be measured by the incidence, nature, and severity of adverse events. The safety outcome measures are the following protocol-specific adverse events:

- Incidence of adverse events and serious adverse events
- Incidence of adverse events leading to T-DM1 discontinuation, modification, or interruption
- Incidence of adverse events leading to trastuzumab discontinuation or interruption
- Incidence of adverse events leading to docetaxel discontinuation, modification, or interruption
- Incidence of CHF and symptomatic decline in LVEF

- Cause of death on study

4.4 EXPLORATORY ENDPOINTS

The exploratory endpoints for this study are as follows:

- Exposure-effect analysis to investigate the relationship between the pharmacokinetics of T-DM1 and drug effect (e.g., efficacy, safety)
- Presence and/or levels of soluble HER2 extracellular domain (ECD) correlated with efficacy

V. REASONS FOR EARLY CESSATION OF TRIAL THERAPY

5.1 PATIENT DISCONTINUATION

The investigator has the right to discontinue a patient from study therapy (a) for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; (b) for reasons of noncompliance (e.g., missed doses, visits); (c) if the patient becomes pregnant; or (d) if the investigator determines it is in the best interest of the patient.

Patients may withdraw from the study or from study therapy at any time. Any patient who withdraws will be asked to return to the study center for a follow-up visit. Patients who discontinue early should return within 30 days following the last dose of study drug for an early termination visit. The primary reason for discontinuation must be recorded on the appropriate electronic Case Report Form (eCRF) page.

Patients must be withdrawn from study therapy if they experience either of the following:

- Disease progression (defined using modified RECIST)
- Toxicity per the parameters specified or other unacceptable toxicity

Other reasons for patient discontinuation may include, but are not limited to, the following:

- Noncompliance
- Investigator decision based on the patient's best interest
- Patient decision
- Patient becomes pregnant

Patients who discontinue from study therapy for any of the above reasons will continue to be followed according to protocol for survival analysis.

5.2 STUDY DISCONTINUATION

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The final analysis has been completed
- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

VI. OBJECTIVES AND ENTIRE STATISTICAL SECTION (INCLUDING ENDPOINTS)

6.1 OBJECTIVES

6.1.1 PRIMARY OBJECTIVES

The primary objectives for this study are as follows:

- To explore the efficacy of T-DM1 compared with the combination of trastuzumab and docetaxel in patients with HER2-positive, unresectable, locally advanced breast cancer and/or metastatic breast cancer who have not received prior chemotherapy for metastatic disease, as measured by PFS based on investigator assessments
- To evaluate the safety of T-DM1 compared with the combination of trastuzumab and docetaxel in this population

6.1.2 SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

- To explore the efficacy of T-DM1 compared with the combination of trastuzumab and docetaxel in patients with HER2-positive, unresectable, locally advanced breast cancer and/or metastatic breast cancer who have not received prior chemotherapy for metastatic disease, as measured by the 12-month PFS rate, median PFS, duration of overall survival, survival rate at 12 months, objective response rate, duration of objective response, and clinical benefit rate (the proportion of patients with CR or PR or stable disease for ≥ 6 months since randomization)
- To characterize the PK properties of T-DM1 in this patient population
- To compare the time to symptom progression, as measured by the TOI-PFB and the Patient's Assessment of Pain, in the two treatment arms

6.1.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- To conduct an exploratory exposure-effect analysis to investigate the relationship between the pharmacokinetics of T-DM1 and drug effect (e.g., efficacy, safety)
- To investigate whether presence and/or levels of soluble HER2 ECD at baseline correlate with efficacy

6.2 STATISTICAL METHODS

This is a Phase II study designed to make a preliminary assessment of the efficacy of T-DM1 (Treatment Arm A) relative to the combination of trastuzumab and docetaxel (Treatment Arm B) in patients with HER2-positive MBC who have not received prior therapy for metastatic disease, as measured by PFS based on investigator assessment. The emphasis of the analyses of efficacy outcomes will be on estimation of the magnitude of the treatment effect; exploratory hypothesis testing will also be performed.

No formal interim analysis is planned; however, data may be summarized for discussion and meetings with health authorities to enable further proceeding with the project. These data summaries will not be used outside of this context. In addition, ongoing safety and preliminary efficacy data (ORR) may be summarized for major medical conferences.

The primary PFS analysis will take place after 72 investigator-assessed PFS events have occurred in the two arms combined. Overall survival, a secondary endpoint, will be performed at the time of the primary analysis for PFS. Further analyses with longer follow-up may be conducted at study closure.

6.2.1 ANALYSIS OF THE CONDUCT OF THE STUDY

Enrollment, patient disposition, study treatment administration, and discontinuations from the study will be summarized. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated. Eligibility exceptions and major protocol deviations will be summarized by treatment arm.

6.2.2 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic variables and baseline characteristics such as age, race, weight, world region (U.S., ex-U.S.), baseline ECOG performance status, prior adjuvant trastuzumab therapy (yes, no), disease-free interval, involvement of visceral sites, and hormonal receptor status will be summarized by treatment arm.

6.2.3 EFFICACY ANALYSES

a. Primary Efficacy Analysis

The primary efficacy analysis will include all randomized patients, following the intent-to-treat (ITT) principle based on the treatment arm to which patients were randomized.

The primary efficacy endpoint is PFS based on investigator assessment, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator tumor assessments using modified RECIST, or death on study from any cause, whichever occurs earlier. Death on study is defined as death from any cause within 30 days of the last dose of study drug prior to crossover. The first documented PD event prior to crossover on the control arm will be included in the analysis of the primary endpoint of PFS.

Data for patients without disease progression or death on study will be censored at the date of the last tumor assessment prior to crossover (or, if no tumor assessments were performed after the baseline visit, at the date of randomization plus 1 day). Data for patients who were lost to follow-up will be censored at the last date of tumor assessment prior to crossover at which the patient was known to be progression free.

Kaplan−Meier estimates of the PFS curve and the median PFS and 12-month PFS rate will be presented for each treatment arm. The hazard ratio (HR) of PFS comparing T-DM1 against the combination of trastuzumab and docetaxel, and its 95% confidence interval (CI) will be estimated from a Cox proportional hazards model, stratified by world region (U.S., ex-U.S.), prior adjuvant trastuzumab therapy (yes, no), and DFI (≤ 24 months or > 24 months). Unstratified analyses will also be performed.

b. Secondary Efficacy Analysis

Overall survival is defined as the time from randomization to the date of death from any cause. Patients who are alive at the time of analysis will be censored at the date on which they were last known to be alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day. Similar to the primary efficacy analysis of PFS, overall survival will be analyzed by Kaplan−Meier methods and stratified Cox proportional model. In addition, the survival rate at 12 months will be provided.

Objective response is defined as partial response plus complete response as determined by investigator tumor assessments using modified RECIST. Objective responses must be confirmed at least 28 days after the initial documentation of response. Only patients with measurable disease at study entry will be included in the analysis of objective response. To be conservative, patients with no post-baseline tumor assessment or who die prior to their first scheduled tumor assessment will be considered non-responders.

An estimate of the objective response rate and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm, along with the difference in objective response rates between the two treatment arms and its 95% CI.

Duration of objective response is defined as the time from first occurrence of a documented objective response until disease progression as determined by investigator tumor assessments using modified RECIST, or death on study from any cause, whichever occurs first. Only patients with an objective response will be included in this analysis.

Data for patients without disease progression or death after occurrence of objective response will be censored at the date of the last tumor assessment after objective response (or, if no tumor assessments were performed after occurrence of objective response, at the date of objective response plus 1 day). Data for patients who were lost to follow-up will be censored at the last date of tumor assessment after objective response (or, if no tumor assessments were performed after occurrence of objective response, at the date of objective response plus 1 day), at which the patient was known to be progression-free.

Similar to the primary efficacy analysis of PFS, duration of objective response will be analyzed by Kaplan−Meier methods and stratified Cox proportional model.

Clinical benefit is defined as objective response (CR or PR) or stable disease for 6 months after randomization as determined by investigator tumor assessments using modified RECIST. Stable disease requires one post-baseline tumor assessment, approximately 9 weeks or more after randomization. Only patients with measurable disease at study entry will be included in the analysis of clinical benefit. To be conservative, patients with no post-baseline tumor assessment or who die prior to their first scheduled tumor assessment will be considered to be non-responders.

An estimate of the clinical benefit rate and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm, along with the difference in clinical benefit rates between the two treatment arms and its 95% CI.

Time to symptom progression is defined as the time from randomization to the first documentation of a ≥ 5-point decrease from baseline in the scoring of responses to the TOI-PFB subscale of the FACT-B questionnaire.

FACT-B, TOI-PFB, and pain intensity score at baseline, change from baseline, and post-baseline values will be summarized by treatment arm.

6.2.4 SAFETY ANALYSES

The safety population will consist of all patients who received any amount of study treatment, with patients allocated to the treatment arm associated with the regimen actually received. Safety of the treatment arms will be assessed using summaries of adverse events, cardiac-specific adverse events, LVEF measurements, laboratory test results, and causes of death. These summaries as well as each of the following safety analyses will be conducted for events with onset on or after the start of treatment and prior to the start of cross-over treatment, or events with unknown onset date.

In addition, each of the following safety analyses will be repeated for patients in Arm B who elect to receive optional crossover T-DM1. The data will be reported for emergent events or for any event of worsening grade occurring on, or subsequent to, the date of the first study treatment of T-DM1.

a. Adverse Events

Adverse events occurring on or after the first study treatment will be summarized by event term and NCI CTCAE, Version 3.0 toxicity grade.

b. Deaths

Deaths reported during the study treatment period and those reported during follow-up after study treatment discontinuation will be summarized by causes and by treatment arm.

c. Laboratory Data

Laboratory abnormalities will be defined based on laboratory normal ranges and NCI CTCAE, Version 3.0. Laboratory abnormalities, such as worst toxicity grade and toxicity grade shift from baseline, will be summarized by treatment arm.

6.2.5 MISSING DATA

For PFS, data for patients who are lost-to-follow-up will be analyzed as censored on the last tumor assessment date at which the patient was known to be progression-free. Data for patients with no post-baseline tumor assessment will be analyzed as censored on the randomization date plus 1 day.

For overall survival, data for patients who are lost to follow-up will be analyzed as censored on the last date that the patient was known to be alive. Protocol: T-DM1—Genentech, Inc. 76/P TDM4450g-A3

For overall response, patients without a post-baseline disease assessment will be considered non-responders.

For the analysis of QOL data, according to the Functional Assessment of Chronic Illness Therapy Measurement System Manual, imputation of missing values will

not be performed. Instead, the scoring procedure specified in the manual pertinent to adjusting for missing values will be used.

6.2.6 DETERMINATION OF SAMPLE SIZE

The emphasis of this Phase II study is estimation of effect size and incidence of adverse events, rather than hypothesis testing. The sample size for this study was estimated from EAST software with the following assumptions.

The study is anticipated to enroll 120 patients over 13 months and followed for an additional 12 months. The accrual rate is assumed to be 0.12 patients per site per month, with 100 sites being initiated over a 6-month ramp-up period. The primary PFS analysis will be performed after 72 PFS events have occurred in the two arms combined.

With 72 PFS events, the 95% CI around the estimated hazard ratio (HR) for comparison of the two treatment arms will be approximately (0.63 × HR, 1.59 × HR). For example, the 95% CI around an estimated HR of 0.67 would be (0.42, 1.06), and the 95% CI around an estimated HR of 0.75 would be (0.47, 1.19). This trial is hypothesis generating and is able to detect only a large benefit of T-DM1 over the combination of trastuzumab and docetaxel. In particular, this trial will not have adequate power to detect minimum clinically meaningful differences between the treatment and control arms. Thus, formal hypothesis testing is limited in that statistically negative outcomes do not necessarily rule out clinically significant treatment effects.

6.2.7 DATA QUALITY ASSURANCE

Data will be collected using an electronic data capture (EDC) system and data will be entered using eCRFs. Only authorized staff at the study site will conduct and be responsible for the data entry. Genentech will be responsible for data

management, including data quality assurance. Some of the data management responsibilities will be outsourced to a contract research organization (CRO). These outsourced activities include quality checking of the data and query management within the EDC system. Genentech will produce an EDC Study Specification document that defines data review procedures, access privileges based on roles, and the automated data checking rules. In order to address data reviewer concerns and discrepancies between site entries and data checking rules, Genentech or the CRO will initiate queries for data clarification from the sites, which the sites will resolve electronically in the EDC system. Laboratory data will be transferred directly to the EDC system, in concordance with Genentech's standard procedures for electronic data transfer. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored in the EDC system will be consistent with the EDC vendor's standard procedures.

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Taxotere® (Docetaxel) Package Insert (Sanofi-Aventis, Inc.)