SYNOPSIS OF CLINICAL STUDY REPORT

Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use Only)
Name of Finished Product: Trastuzumab emtansine	**Volume:**	
Name of Active Ingredient: T-DM1	**Page:**	

Title of Study: An Expanded Access, Open-Label Study of Trastuzumab Emtansine Administered Intravenously to Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer

Phase of Development: IIb

Study Period: 7 June 2010 (First Patient First Visit [FPFV]) to 7 May 2013 (Last Patient Last Visit [LPLV]).

Objectives

Primary:

- To assess the safety of trastuzumab emtansine administered to patients with HER2-positive locally advanced or metastatic breast cancer

Secondary:

- To assess the efficacy of trastuzumab emtansine in patients with HER2-positive locally advanced or metastatic breast cancer, as measured by objective response rate (complete response [CR] + partial response [PR]) in patients with measurable disease, based on investigator assessment using Response Evaluation Criteria In Solid Tumor, version 1.1 [RECIST v1.1])

Methodology

This was a multicenter, open-label, single-arm, expanded-access study designed to provide trastuzumab emtansine (administered at a dose of 3.6 mg/kg) to patients with HER2-positive locally advanced or metastatic breast cancer and to evaluate the safety and efficacy of trastuzumab emtansine administered by intravenous (IV) infusion. Patients received trastuzumab emtansine in 3-week cycles. The primary goal of this study was to provide trastuzumab emtansine to patients until trastuzumab emtansine became commercially available.

Details of the study can be found in the protocol (see Appendix 11.1.1).

Efficacy Evaluations

The efficacy-evaluable population included 252/335 patients (75.2%) who received at least one dose of trastuzumab emtansine and had at least one follow-up tumor assessment or who died within 30 days after the last dose of the study drug.

See Section 7 for details on efficacy results.

Safety Evaluations

All 335 patients received at least one dose of study drug and were included in the safety-evaluable population.

See Section 8 for details on the safety results.

Overall Summary and Conclusions

Trastuzumab emtansine 3.6 mg/kg given every 3 weeks was generally well tolerated in patients with HER2-positive, recurrent, locally advanced or metastatic breast cancer in this expanded access study. The most common safety events were similar to those expected and reported with single-agent trastuzumab emtansine (Verma et al. 2012; Krop et al. 2012), and no new safety concerns were identified in this study.

A total of 322 (96.1%) patients experienced at least one treatment-emergent AE. The most frequent AEs were fatigue, nausea, dry mouth, headache, pyrexia, constipation, vomiting, epistaxis, thrombocytopenia, cough, hypokalemia, increased AST, decreased appetite, back pain, diarrhea, and upper respiratory tract infection. These results are similar to results from EMILIA in which 95.9% experienced at least one AE; the most common AEs were nausea, fatigue, thrombocytopenia, diarrhea, elevated AST, elevated ALT, and vomiting. In the Phase II study (TDM4374g), all patients experienced at least one AE.

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There were 280 (83.6%) patients with AEs that were considered to be related to study drug. The most common treatment-emergent AEs considered related to trastuzumab emtansine administration were primarily Grades 1 and 2 and were fatigue, nausea, thrombocytopenia, dry mouth, epistaxis, and pyrexia.

A total of 61 (18.2%) patients experienced an SAE; only 8 (2.4%) patients had SAEs that were considered to be related to study drug. Of 335 patients, 137 (40.9%) patients had an AE of Grade $\geq$ 3 and 15 (4.5%) discontinued study drug due to AEs. These results are similar to the findings in the EMILIA study, in which 15.5% of patients experienced an SAE and 41% had Grade 3 or 4 AEs as well as the Phase II study (TDM4374g), in which 22.7% patients had an SAE and 44.5% had a Grade $\geq$ 3 AE.

There were no Grade $\geq$ 3 AESIs of left ventricular systolic dysfunction compared to 1 patient with Grade 3 left ventricular systolic dysfunction in the EMILIA study. Twelve (3.6%) patients had LVEF $\leq$ 45% as assessed by ECHO or MUGA scan; these results are only slightly worse than those from the EMILIA study, in which 2.9% had an LVEF $\leq$ 45%.

Of 252 efficacy-evaluable patients, 46 (18.3%) patients (4 [6%] CRs and 42 [16.7%] PRs) had a confirmed overall response per RECIST v1.1 and the clinical benefit rate was 31.7% in the efficacy evaluable population. Of 252 efficacy-evaluable patients, 68 (27.0%) had PD. The ORR in this study was lower than the ORR reported in the EMILIA study (ORR = 43.6%) and in Study TDM4374g (ORR = 32.7%). This was expected as the majority of the patients included in the efficacy analyses (202 [80.2%]) were enrolled before Amendment 3 and therefore included patients who were more heavily pre-treated than those enrolled in the EMILIA study or Study TDM4374g. In addition, the study duration was substantially shorter compared to the EMILIA study (median follow-up was 2.8 months for all patients and 5.9 months for patients enrolled before Amendment 3, compared with 12.9 months in T-DM1 group in the EMILIA study).

In conclusion:

- In the setting of this expanded access study, trastuzumab emtansine had similar safety and lower efficacy profiles to those previously reported in other trastuzumab emtansine Phase II (TDM4374g) and III (TDM4370g/EMILIA) clinical trials.
- Although patients in Study TDM4884g were heavily pretreated (median of seven prior therapies for HER2-positive metastatic breast cancer and a median of 38 months from initial metastatic diagnosis to enrollment), significant activity was still observed with trastuzumab emtansine.
- Limitations of this study were that patients were enrolled and monitored under less stringent criteria than in a registrational clinical trial, including: investigator assessment of response; no central review of pathology, cardiac imaging, or radiological imaging; less detailed reporting criteria; and less stringent timing of assessments.
- Despite multiple lines of prior treatment, trastuzumab emtansine dose reductions were minimal. The percentage of dose reductions in this study (14.6%) was similar to that reported for the less pretreated population of patients in the Phase III EMILIA study (16.3%; Verma et al. 2012).
- The results of this expanded access study in a more heavily pretreated population suggest that the full dose of trastuzumab emtansine at 3.6 mg/kg every 3 weeks is feasible in patients with pretreated HER2-positive metastatic breast cancer, with no new safety concerns.

Date of the Report

16 December 2013