Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D.,
José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D.,
Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D.,
and Kim Blackwell, M.D., for the EMILIA Study Group

ABSTRACT

BACKGROUND

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate incorporating the human epidermal growth factor receptor 2 (HER2)–targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. The antibody and the cytotoxic agent are conjugated by means of a stable linker.

METHODS

We randomly assigned patients with HER2-positive advanced breast cancer, who had previously been treated with trastuzumab and a taxane, to T-DM1 or lapatinib plus capecitabine. The primary end points were progression-free survival (as assessed by independent review), overall survival, and safety. Secondary end points included progression-free survival (investigator-assessed), the objective response rate, and the time to symptom progression. Two interim analyses of overall survival were conducted.

RESULTS

Among 991 randomly assigned patients, median progression-free survival as assessed by independent review was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine (hazard ratio for progression or death from any cause, 0.65; 95% confidence interval [CI], 0.55 to 0.77; P<0.001), and median overall survival at the second interim analysis crossed the stopping boundary for efficacy (30.9 months vs. 25.1 months; hazard ratio for death from any cause, 0.68; 95% CI, 0.55 to 0.85; P<0.001). The objective response rate was higher with T-DM1 (43.6%, vs. 30.8% with lapatinib plus capecitabine; P<0.001); results for all additional secondary end points favored T-DM1. Rates of adverse events of grade 3 or above were higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1, whereas the incidences of diarrhea, nausea, vomiting, and palmar–plantar erythrodysesthesia were higher with lapatinib plus capecitabine.

CONCLUSIONS

T-DM1 significantly prolonged progression-free and overall survival with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane. (Funded by F. Hoffmann–La Roche/Genentech; EMILIA ClinicalTrials.gov number, NCT00829166.)

From Sunnybrook Odette Cancer Centre, Toronto (S.V.); Mount Vernon Cancer Centre, Northwood, United Kingdom (D.M.); San Raffaele Hospital, Milan (L.G.); Dana–Farber Cancer Institute (I.E.K.) and Massachusetts General Hospital (J.B.) — both in Boston; Medical Office Hematology, Aschaffenburg, Germany (M.W.); University of Miami Sylvester Comprehensive Cancer Center, Miami (M.P.); Seoul National University College of Medicine, Seoul, South Korea (D.-Y.O.); Institut Curie, Paris (V.D.); Genentech, South San Francisco, CA (E.G., L.F., M.W.L., S.O.); and Duke University Medical Center, Durham, NC (K.B.). Address reprint requests to Dr. Verma at Sunnybrook Odette Cancer Centre, 2075 Bayview Ave., Toronto, ON M4N 3M5, Canada, or at sunil.verma@sunnybrook.ca.

AMPLIFICATION OF HUMAN EPIDERMAL growth factor receptor 2 (HER2, also called ErbB2) occurs in approximately 20% of breast cancers and is associated with shortened survival.[1-3] Combining HER2-targeted agents with standard chemotherapy is an effective therapeutic approach for patients with HER2-positive metastatic breast cancer. When combined with first-line chemotherapy, trastuzumab increases the time to progression and overall survival among patients with metastatic disease.[4,5] The addition of lapatinib to capecitabine increases the time to progression in patients previously treated with trastuzumab, an anthracycline, and a taxane,[6] and this combination is a standard option for disease progression with trastuzumab.

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate that incorporates the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine); the antibody and the cytotoxic agent are conjugated by means of a stable linker.[7,8] T-DM1 allows intracellular drug delivery specifically to HER2-overexpressing cells, thereby improving the therapeutic index and minimizing exposure of normal tissue. Phase 2 studies have shown the clinical activity of T-DM1 in patients with HER2-positive advanced breast cancer.[9-11]

The EMILIA study, a phase 3 trial, assessed the efficacy and safety of T-DM1, as compared with lapatinib plus capecitabine, in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.

METHODS

STUDY DESIGN

The EMILIA study is a randomized, open-label, international trial involving patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer who were previously treated with trastuzumab and a taxane. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice standards and the Declaration of Helsinki. Patients provided written informed consent; the study was approved by the relevant institutional review board or independent ethics committee.

Patients were randomly assigned in a 1:1 ratio to T-DM1 or lapatinib plus capecitabine with the use of a hierarchical, dynamic randomization scheme through an interactive voice-response system. Stratification factors were world region (United States, Western Europe, or other), the number of prior chemotherapy regimens for unresectable, locally advanced or metastatic disease (0 or 1 vs. >1), and disease involvement (visceral vs. nonvisceral).

The primary end points were progression-free survival assessed by independent review, overall survival, and safety. Progression-free survival was defined as the time from randomization to progression or death from any cause. Progression was assessed according to modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0[12]; the modified criteria are specified in the Supplementary Appendix, available with the full text of this article at NEJM.org. Overall survival was defined as the time from randomization to death from any cause. Prespecified secondary end points included progression-free survival (investigator-assessed), the objective response rate, the duration of response, and the time to symptom progression. The objective response rate was determined according to modified RECIST on the basis of an independent review of patients with measurable disease at baseline; responses were confirmed at least 28 days after the initial documentation of a response. The time to symptom progression was defined as the time from randomization to the first decrease of 5 points or more from baseline scores on the Trial Outcome Index of the patient-reported Functional Assessment of Cancer Therapy–Breast (FACT-B TOI, on which scores range from 0 to 92, with higher scores indicating a better quality of life)[13] in women with a baseline score and at least one postbaseline score. Safety was monitored by an independent data monitoring committee and a cardiac review committee.

STUDY OVERSIGHT

The study was designed by the academic investigators, the trial steering committee, and representatives of the sponsor, F. Hoffmann–La Roche/Genentech. The data were collected by the sponsor and analyzed in collaboration with the authors, who vouch for the accuracy and completeness of the data and analysis and the fidelity of the study to the protocol, available at NEJM.org. The first author prepared the initial draft of the manuscript with support from a medical writer who was paid by Genentech. All the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication.

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PATIENTS

Eligible patients had documented progression of unresectable, locally advanced or metastatic HER2-positive breast cancer previously treated with a taxane and trastuzumab. Inclusion criteria were progression during or after the most recent treatment for locally advanced or metastatic disease or within 6 months after treatment for early-stage disease, and a centrally confirmed HER2-positive status, assessed by means of immunohistochemical analysis (with 3+ indicating positive status), fluorescence in situ hybridization (with an amplification ratio ≥2.0 indicating positive status), or both. Patients with measurable disease (according to modified RECIST) and those with nonmeasurable disease were included. Other eligibility criteria were a left ventricular ejection fraction of 50% or more (determined by echocardiography or multiple-gated acquisition [MUGA] scanning) and an Eastern Cooperative Oncology Group performance status of 0 (asymptomatic) or 1 (restricted in strenuous activity but ambulatory and able to do light work).

Major exclusion criteria were prior treatment with T-DM1, lapatinib, or capecitabine; peripheral neuropathy of grade 3 or higher (according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 3.0)[14]; symptomatic central nervous system (CNS) metastases or treatment for these metastases within 2 months before randomization; a history of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment; and a history of myocardial infarction or unstable angina within 6 months before randomization.

PROCEDURES

Patients in the control group self-administered oral lapatinib at a dose of 1250 mg daily plus oral capecitabine at a dose of 1000 mg per square meter of body-surface area every 12 hours (maximum planned daily dose, 2000 mg per square meter) on days 1 through 14 of each 21-day treatment cycle and recorded their doses in a patient diary. Dose delays, reductions, and discontinuations owing to toxic effects were defined in the protocol. For capecitabine, the first dose reduction was to 75% of the total daily dose, and the second to 50% of that dose (see Table 1 in the Supplementary Appendix). For lapatinib, the first dose reduction was to 1000 mg daily, and the second to 750 mg daily. Patients could continue to take lapatinib if capecitabine was discontinued and vice versa. If treatment with both drugs was delayed for more than 42 consecutive days, the drugs were discontinued.

Patients randomly assigned to T-DM1 received 3.6 mg per kilogram of body weight intravenously every 21 days. Dose delays, reductions, and discontinuations owing to toxic effects were defined in the protocol. The first dose reduction was to 3.0 mg per kilogram and the second to 2.4 mg per kilogram (Table 1 in the Supplementary Appendix). Dose escalation was not allowed after a dose reduction. If a toxic event did not resolve to a grade 1 level or to baseline status within 42 days after the most recent dose, the study treatment was discontinued. Patients continued to receive the study treatment until disease progression (investigator-assessed) or the development of unmanageable toxic effects.

ASSESSMENTS

Tumor assessments were performed by the study investigators and by the independent review committee at baseline and every 6 weeks thereafter until investigator-assessed disease progression; an additional assessment was required 6 weeks after progression. The left ventricular ejection fraction was measured by means of echocardiography (the preferred method) or MUGA scanning at baseline, week 6, week 12, and every 12 weeks thereafter until discontinuation of the study treatment; an additional assessment was performed 30 days after the last dose of the study drug. Local laboratory assessments were performed at baseline, on day 1 of each treatment cycle, on days 8 and 15 of cycles 1 through 4, and 30 days after the last dose of the study drug. Adverse events were monitored continuously and graded according to the CTCAE, version 3.0.

STATISTICAL ANALYSIS

The trial was originally designed with progression-free survival, as assessed by independent review, as the primary efficacy end point, with a planned sample of 580 patients. In October 2010, with all data still masked to the investigators, the protocol was amended to add overall survival as a coprimary efficacy end point, with an increase in the planned sample to 980 patients. The trial had 90% power to detect a hazard ratio of 0.75 for progression or death from any cause with T-DM1 as compared with lapatinib plus capecitabine and 80% power to detect a hazard ratio of 0.80 for death from any cause, with a two-sided alpha level of 0.05.

The primary analysis of progression-free survival was to be performed after 508 independently assessed events, and the final analysis of overall survival after 632 deaths. The first interim analysis of overall survival was to be performed at the time of the primary analysis of progression-free survival. A second interim analysis was added to the statistical analysis plan after the completion of the first interim analysis and was conducted when 50% of the targeted events had occurred. Stopping boundaries for efficacy were determined by means of the Lan–DeMets alpha-spending function with an O'Brien–Fleming boundary and the actual number of observed deaths. To adjust for multiple comparisons, a fixed-sequence hypothesis-testing procedure was implemented. The hypothesis test for progression-free survival was conducted at a two-sided alpha level of 0.05. If the result was statistically significant, overall survival was to be tested at a two-sided alpha level of 0.05, which was spent at the interim and final analyses according to the Lan–DeMets spending function. If both primary end points were statistically significant, the secondary end points were to be tested in a prespecified order. The statistical analysis plan is included in the protocol.

The primary end points were assessed in the intention-to-treat population and tested by means of two-sided log-rank tests, with stratification according to the factors used for randomization. A sensitivity analysis was performed for progression-free survival among patients who received nonprotocol breast-cancer treatment before documented disease progression, with censoring of data at the last tumor assessment before the initiation of such therapy. Kaplan–Meier methods were used to estimate medians for the primary end points, 1- and 2-year survival rates, and corresponding 95% confidence intervals. Analyses of progression-free survival in 16 prespecified subgroups were performed. Ten post hoc analyses to assess potential effects of prior therapy were performed. All post hoc analyses had similar results, and the results of one representative analysis (line of therapy) are therefore reported here. We used a Cox proportional-hazards model, with the same stratification factors as those used for randomization, to estimate hazard ratios and 95% confidence intervals for the primary efficacy end points and for subgroup analyses.

Investigator-assessed progression-free survival and the time to symptom progression were analyzed with the same methods as those used for independent review. The objective response rate was compared between groups with the use of the Mantel–Haenszel chi-square test, with stratification according to the factors used for randomization. For patients with an objective response, the median duration of the response was estimated with the use of the Kaplan–Meier approach.

RESULTS

STUDY POPULATION

From February 2009 through October 2011, a total of 991 patients were enrolled at 213 centers in 26 countries; 496 patients were assigned to lapatinib plus capecitabine, and 495 were assigned to T-DM1 (Fig. 1 in the Supplementary Appendix). Baseline demographic and disease characteristics were similar in the two groups (Table 1; see Table 2 in the Supplementary Appendix for additional baseline information). The first data-cutoff date of January 14, 2012 (median duration of follow-up, approximately 13 months), was used for all analyses in this report except the second interim analysis of overall survival, which had a data-cutoff date of July 31, 2012 (median duration of follow-up, approximately 19 months).

PRIMARY ANALYSIS

Treatment with T-DM1 significantly improved progression-free survival as assessed by independent review (median survival, 9.6 months, vs. 6.4 months with lapatinib plus capecitabine; stratified hazard ratio for progression or death from any cause, 0.65; 95% confidence interval [CI], 0.55 to 0.77; P<0.001) (Fig. 1) and in the sensitivity analysis with censoring for nonprotocol therapy (Table 3 in the Supplementary Appendix). This benefit was consistently observed across clinically relevant subgroups, with a less definitive benefit among patients 75 years of age or older and those with nonvisceral or nonmeasurable disease (Fig. 2 in the Supplementary Appendix).

At the first interim analysis of overall survival (223 deaths), the stratified hazard ratio for death from any cause with T-DM1 versus lapatinib plus capecitabine was 0.62 (95% CI, 0.48 to 0.81; P=0.0005) and did not cross the predefined O'Brien–Fleming stopping boundary (P=0.0003).

Table 1. Selected Demographic and Baseline Characteristics of the Patients.*

Characteristic	Lapatinib plus Capecitabine (N = 496)	T-DM1 (N = 495)
Age — yr		
Median	53	53
Range	24–83	25–84
Race — no. (%)†		
White	374 (75)	358 (72)
Asian	86 (17)	94 (19)
Black	21 (4)	29 (6)
Other	10 (2)	7 (1)
Not available	5 (1)	7 (1)
World region — no. (%)		
United States	136 (27)	134 (27)
Western Europe	160 (32)	157 (32)
Asia	76 (15)	82 (17)
Other	124 (25)	122 (25)
ECOG performance status — no. (%)‡		
0	312 (63)	299 (60)
1	176 (35)	194 (39)
Not available	8 (2)	2 (<1)
Site of disease involvement — no. (%)		
Visceral	335 (68)	334 (67)
Nonvisceral	161 (32)	161 (33)
Hormone-receptor status — no. (%)		
ER-positive, PR-positive, or both	263 (53)	282 (57)
ER-negative and PR-negative	224 (45)	202 (41)
Unknown	9 (2)	11 (2)
Prior systemic therapy — no. (%)§		
Anthracycline	302 (61)	303 (61)
Other chemotherapy	382 (77)	385 (78)
Biologic agent other than trastuzumab or pertuzumab	21 (4)	13 (3)
Endocrine therapy	204 (41)	205 (41)
Prior chemotherapy regimens for locally advanced or metastatic disease — no. (%)		
0 or 1	305 (61)	304 (61)
>1	191 (39)	191 (39)
Prior trastuzumab treatment — no. (%)§		
For metastatic breast cancer, early breast cancer, or both	419 (84)	417 (84)
For early breast cancer only	77 (16)	78 (16)

* ER denotes estrogen receptor, PR progesterone receptor, and T-DM1 trastuzumab emtansine.
† Race was self-reported.
‡ An Eastern Cooperative Oncology Group (ECOG) performance status of 0 indicates that the patient is asymptomatic, and a status of 1 indicates that the patient is restricted in strenuous activity but ambulatory and able to do light work.
§ The study protocol specified that previous treatment with a taxane and trastuzumab was required for enrollment.

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