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ORIGINAL REPORT

Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Administered As First-Line Treatment: The M77001 Study Group

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
This randomized, multicenter trial compared first-line trastuzumab plus docetaxel versus docetaxel alone in patients with human epidermal growth factor receptor 2 (HER2) –positive metastatic breast cancer (MBC).

Patients and Methods
Patients were randomly assigned to six cycles of docetaxel 100 mg/m^2 every 3 weeks, with or without trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly until disease progression.

Results
A total of 186 patients received at least one dose of the study drug. Trastuzumab plus docetaxel was significantly superior to docetaxel alone in terms of overall response rate (61% *v* 34%; $P = .0002$), overall survival (median, 31.2 *v* 22.7 months; $P = .0325$), time to disease progression (median, 11.7 *v* 6.1 months; $P = .0001$), time to treatment failure (median, 9.8 *v* 5.3 months; $P = .0001$), and duration of response (median, 11.7 *v* 5.7 months; $P = .009$). There was little difference in the number and severity of adverse events between the arms. Grade 3 to 4 neutropenia was seen more commonly with the combination (32%) than with docetaxel alone (22%), and there was a slightly higher incidence of febrile neutropenia in the combination arm (23% *v* 17%). One patient in the combination arm experienced symptomatic heart failure (1%). Another patient experienced symptomatic heart failure 5 months after discontinuation of trastuzumab because of disease progression, while being treated with an investigational anthracycline for 4 months.

Conclusion
Trastuzumab combined with docetaxel is superior to docetaxel alone as first-line treatment of patients with HER2-positive MBC in terms of overall survival, response rate, response duration, time to progression, and time to treatment failure, with little additional toxicity.

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is a key contributor to normal cell growth and differentiation.[1] However, when overexpressed, it is associated with neoplastic transformation of cells. Approximately 15% to 20% of breast cancers show HER2 overexpression (3+ by immunohistochemistry [IHC]) and/or amplification of the *HER2* gene. HER2-positive malignancies have a significantly more aggressive disease

course and lead to a worse clinical outcome, including shortened overall survival (OS), compared with those that do not overexpress HER2.[2,3] Trastuzumab is a humanized murine monoclonal antibody that binds specifically to the extracellular domain of the HER2 protein. The clinical efficacy and favorable safety profile of trastuzumab in metastatic breast cancer (MBC) have been demonstrated when administered as monotherapy[4,5] and in combination with the taxane paclitaxel.[6] Clinical benefits are greatest in patients with tumors strongly overexpressing HER2, graded 3+ by IHC, and/or with *HER2* gene amplification, as determined by fluorescence in situ hybridization (FISH). In a randomized phase III trial (study H0648g), which compared trastuzumab plus paclitaxel with paclitaxel alone, the median OS in patients with IHC 3+ disease was 40% longer in the combination arm than in the paclitaxel-alone arm (24.8 *v* 17.9 months),[6,7] highlighting the benefit of combining trastuzumab with paclitaxel.

Docetaxel is another widely used taxane and has a similar mechanism of action to that of paclitaxel. It is one of the most active chemotherapeutic agents used in the treatment of MBC.[8,9] Preclinical data indicate synergy between docetaxel and trastuzumab,[10] and clinical activity has been confirmed in a number of phase II studies, with response rates of 44% to 83% and toxicity comparable with that of single-agent docetaxel.[11-22]

The preclinical data, the known clinical activity of trastuzumab plus paclitaxel, and the favorable results of phase II trials of trastuzumab plus docetaxel provided a strong rationale for investigating trastuzumab and docetaxel in a randomized trial. Study M77001 was designed to compare the overall response rate (ORR) of trastuzumab plus docetaxel versus docetaxel alone. The trial also aimed to characterize the safety profile of trastuzumab in combination with docetaxel versus docetaxel alone, and to compare duration of response (DR), time to disease progression (TTP), time to treatment failure (TTF), and OS in the two treatment arms.

PATIENTS AND METHODS

Study Design

M77001 is an open-label, comparative, randomized, multicenter, multinational trial comparing the efficacy and safety of first-line trastuzumab (Herceptin, F. Hoffmann-La Roche, Basel, Switzerland) plus docetaxel (Taxotere, Aventis Pharma, Strasbourg, France) with docetaxel alone in patients with HER2-positive MBC. Patients were enrolled onto the trial in 11 European countries and Australia between April 2000 and October 2002. Random assignment to treatment was conducted by block by country. The cutoff point for data reported here is 24 months after enrollment of the last patient.

Patients

Women age 18 to 70 years with HER2-positive MBC were eligible for the trial. Initially, women with IHC 2+ and 3+ disease could be enrolled onto the trial. However, data from other trials indicated that patients with strong HER2 overexpression (IHC 3+) and/or gene amplification (FISH positive) gain the greatest clinical benefit from trastuzumab. This led to a protocol amendment to restrict entry to women with IHC 3+ and/or FISH-positive disease. Patients who had received prior chemotherapy for their metastatic disease or any prior taxanes or anti-HER therapy were excluded. Patients could have received prior (neo) adjuvant anthracyclines (maximum cumulative dose, 360 mg/m^2 doxorubicin or 750 mg/m^2 epirubicin). Baseline left ventricular ejection fraction (LVEF) had to be more than 50%. Hormonal therapy had to be discontinued before the first dose of study drug. Previous radiotherapy was allowed only if treatment had ended at least 14 days before enrollment onto the trial and the patient had fully recovered from all acute adverse effects. Eligible patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, life expectancy ≥ 12 weeks, and at least one bidimensionally measurable lesion (according to WHO criteria). Bone marrow, renal, and hepatic function had to meet the following criteria: hemoglobin $\geq$ 10 g/dL and no blood transfusion within the previous 2 weeks; neutrophil count $\geq 2.0 \times 10^9$ cells/L; platelet count $\geq 100 \times 10^9$ cells/L; no evidence of myelodysplastic syndrome or abnormal bone marrow reserve; creatinine $\leq 1.5 \times$ upper limit of normal (ULN) or creatinine clearance $\geq$ 60 mL/min; total bilirubin less than 1 $\times$ ULN; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN; and alkaline phosphatase $\leq 5 \times$ ULN (patients with AST and/or ALT $> 1.5 \times$ ULN concomitantly with alkaline phosphatase $> 2.5 \times$ ULN were ineligible for the study). Serum calcium had to be less than 2.8 μM/L/mL at enrollment.

Patients who had brain or leptomeningeal metastases were not eligible for the trial. Patients who had significant cardiac insufficiency (New York Heart Association III or IV), myocardial infarction within the previous 6 months, unstable angina pectoris, uncontrolled arrhythmia, or advanced pulmonary disease or severe dyspnea at rest due to complications of advanced malignancy, or who required supplementary oxygen therapy, were also ineligible for the trial.

Treatment

Docetaxel was to be administered for six cycles at 100 mg/m^2 intravenously every 3 weeks. Trastuzumab was to be administered as a 4 mg/kg intravenous loading dose followed by 2 mg/kg weekly until disease progression. All patients received corticosteroid premedication for the docetaxel infusions, which could include dexamethasone, methylprednisolone, or prednisolone. Patients could receive docetaxel beyond six cycles at the discretion of the investigator. After withdrawal from trial M77001, patients were treated at the discretion of the investigator. Patients experiencing disease progression while receiving docetaxel alone were offered the option to cross over to receive trastuzumab. However, the onset and duration of this therapy was not recorded.

Efficacy Assessments

Tumor response was assessed every third cycle by x-ray, computed tomography scan, magnetic resonance imaging, or clinical examination using the WHO criteria. Patients who did not experience disease progression after 1 year in the main study were observed every 3 weeks until disease progression in an extension phase of the study. For patients with an objective response (complete response [CR] or partial response [PR]) or stable disease, radiologic response was also assessed by an independent radiologic reviewer (IRR). Differences between the IRR and

investigator-assessed best response were reconciled manually by comparison of radiologic assessments and measurements between the IRR and investigator, in which IRR assessments always prevailed. Clinical data were also taken into account (which were not available to the IRR). Subgroup analyses were performed to assess the response rate in relation to IHC 3+ and/or FISH-positive measurable disease, prior adjuvant anthracycline therapy, number of metastatic organ sites, presence of visceral metastases, estrogen receptor (ER) and/or progesterone receptor (PgR) status, age, disease-free interval, and ECOG performance status.

Safety Assessments

Adverse events were assessed every cycle for the duration of the trial and graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0. Data on serious adverse events (SAEs) were collected throughout the study, and data on any drug-related SAEs continued to be collected thereafter. Laboratory assessment of blood counts, clinical chemistry, and liver function was carried out before each cycle and ad hoc as clinically indicated. LVEF was assessed by echocardiography or multiple-gated acquisition scan every third cycle.

Statistical Analyses

The assumption was made that a difference of 15% was to be observed in the ORR between the two arms (from 25% in the docetaxel-alone arm to 40% in the docetaxel plus trastuzumab arm). Using the method of Hauck-Anderson, a sample size of 70 assessable patients per arm would allow this difference to be reported with a precision of ± 16.1%, hence giving a 95% CI for the difference in ORR of −1.1% to +31.1%. To allow for nonassessable patients, the total number of patients required for random assignment to treatment was 186 (93 per arm). For response end points, response rates and 95% CI were calculated, with differences between groups tested at the 5% significance level by a two-sided χ^2 test. Response rate differences in various subgroups were presented in a Forest plot, showing odds ratios and 95% confidence limits for treatment differences in each subgroup. For time to event end points, Kaplan-Meier curves were calculated, with differences between groups tested at the 5% significance level by a two-sided log-rank test. Retrospectively, Kaplan-Meier curves were calculated for the subgroup of patients in the docetaxel-alone arm who crossed over to trastuzumab and those who did not cross over.

Conduct of Study

Written informed consent was obtained from all patients before enrollment and the study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice and the principles of the Declaration of Helsinki on the rights of research participants.

RESULTS

Patient Demographics

One hundred eighty-eight patients were randomly assigned to study medication; 94 patients were assigned in each arm. Two patients (both in the trastuzumab plus docetaxel arm) withdrew before receiving the first dose. Baseline patient characteristics (Table 1) were generally balanced between the two arms, although there were more patients with ER- or PgR-positive disease in the docetaxel-alone arm compared with the combination arm (56% *v* 41%), and more patients had received prior (neo)adjuvant anthracyclines in the combination arm compared with the docetaxel-alone arm (64% *v* 55%). Ninety-five percent of patients had IHC 3+ and/or FISH-positive disease; 87% had IHC 3+ disease. The median duration of primary disease (first diagnosis to diagnosis of metastasis) was 26.6 and 22.6 months, and the median duration of metastatic disease was 1.3 months and 1 month, in the combination arm and the docetaxel-alone arm, respectively. A small number of patients, who had a prolonged duration of metastatic disease before study entry, had received hormonal anticancer therapy in the metastatic setting.

Efficacy

Exposure to docetaxel was similar in the two treatment arms. There was a median number of six treatment cycles in both arms (range, one to 14 in the docetaxel-alone arm and one to 15 in the combination arm). More than six cycles of docetaxel were administered to 36 patients (38%) in the docetaxel-alone arm and 30 patients (33%) in the combination arm. The median cumulative dose of docetaxel was 1,044 mg (range, 47 to 2,280 mg) in the docetaxel-alone arm and 1,018 mg (range, 130 to 2,856 mg) in the combination arm. The median number of trastuzumab infusions was 39 (range, one to 171), with a median cumulative dose of 5,044 mg (range, 204 to 25,308 mg).

In the intent-to-treat (ITT) analysis, the ORR in the combination arm was 61% (95% CI, 50% to 71%), comprising six CRs (7%) and 50 PRs (54%) compared with an ORR of 34% (95% CI, 25% to 45%) in the docetaxel-alone arm, comprising two CRs (2%) and 30 PRs (32%; $P = .0002$; Table 2). Stable disease was seen in 27% (95% CI, 18% to 37%) and 44% (95% CI, 33% to 54%) of patients in the combination and docetaxel-alone arms, respectively. Seven patients in the docetaxel-alone arm withdrew at cycle 1 or 2: four withdrew as a result of adverse events; one was treated at another hospital; one withdrew when she was found to have disease that was IHC 2+ and FISH negative; and one withdrew when it was found that she had had abnormal baseline liver function tests. A sensitivity analysis was carried out, with all seven of these patients classified as responders and again with all seven excluded from the ITT population, and in both scenarios the difference in ORR between the arms remained significant.

In all subgroups analyzed (exposure to [neo]adjuvant anthracyclines, number of metastatic organ sites, presence of lung and liver metastases, hormone-receptor status, age, disease-free interval, and ECOG performance status), the response rate in the combination arm was superior to that in the docetaxel-alone arm (Fig 1).

There was a statistically significant superiority ($P = .0325$) in OS for trastuzumab plus docetaxel compared with docetaxel alone (Fig 2). Median OS, estimated by the Kaplan-Meier method, was 31.2 months for trastuzumab

Table 1. Patient Characteristics at Baseline (n = 186)

Characteristic	Trastuzumab + Docetaxel (n = 92)		Docetaxel Alone (n = 94)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	53		55	
Range	32-80		24-79	
HER2 status				
IHC 3+	81	88	82	87
FISH positive	11	12	9	10
IHC 3+ and/or FISH positive	89	97	88	94
Other*	3	3	6	6
Hormone receptor status				
ER positive and/or PgR positive	38	41	53	56
ECOG status				
Median	0		0	
Range	0-4		0-2	
Metastases				
No. lesions/patient				
Median	4		4	
Range	1-12		1-12	
No. sites/patient				
Median	2		2	
Range	1-5		1-5	
Duration primary disease, months				
Median	26.6		22.6	
Range	0.3-267.3		0.2-175.2	
Duration metastatic disease, months				
Median	1.3		1.0	
Range	0.1-67.9		0-66.8	
Site				
Lung	37	40	40	43
Liver	45	49	50	54
Bone	31	34	35	38
Soft tissue	44	48	46	50
Other†	55	60	55	59
Prior therapy				
Adjuvant chemotherapy	65	71	64	68
Adjuvant anthracyclines	59	64	52	55
Hormonal therapy	40	44	44	47
Radiotherapy	59	64	62	66

Abbreviations: HER2, human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization; ER, estrogen receptor; PrG, progesterone receptor; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry.

*Of the nine patients in Other category (without IHC 3+ and/or FISH-positive disease), three in the combination arm and five in the docetaxel-alone arm had IHC 2+/FISH-negative disease and one patient in the docetaxel-alone arm had IHC 0/1+ disease and unknown FISH status.

†Other sites of disease included lymph nodes.

plus docetaxel compared with 22.7 months for docetaxel alone. All other time-to-event analyses also favored the trastuzumab plus docetaxel arm: DR (median, 11.7 *v* 5.7 months; $P = .009$); TTP (median, 11.7 *v* 6.1 months; $P = .0001$); and TTF (median, 9.8 *v* 5.3 months; $P = .0001$; Table 2). In total, 41% of patients in the combination arm and 37% of patients in the docetaxel-alone arm were still alive at the data cutoff date. Median follow-up was 40.9 and 35.9 months in the combination and docetaxel-alone arms, respectively.

Fifty-three patients (57%) in the docetaxel-alone arm were reported to have crossed over to receive trastuzumab, usually at disease progression (30 patients) but in some cases after discontinuation of docetaxel because of toxicity (10 patients) or other reasons (13 patients). The median estimated OS in patients who received docetaxel only was 16.6 months, and it was 30.3 months for patients who crossed over to receive trastuzumab at any time point after withdrawal from this trial (Fig 3).

Safety

Adverse events. All 186 patients who received at least one cycle of treatment were included in the safety analysis.

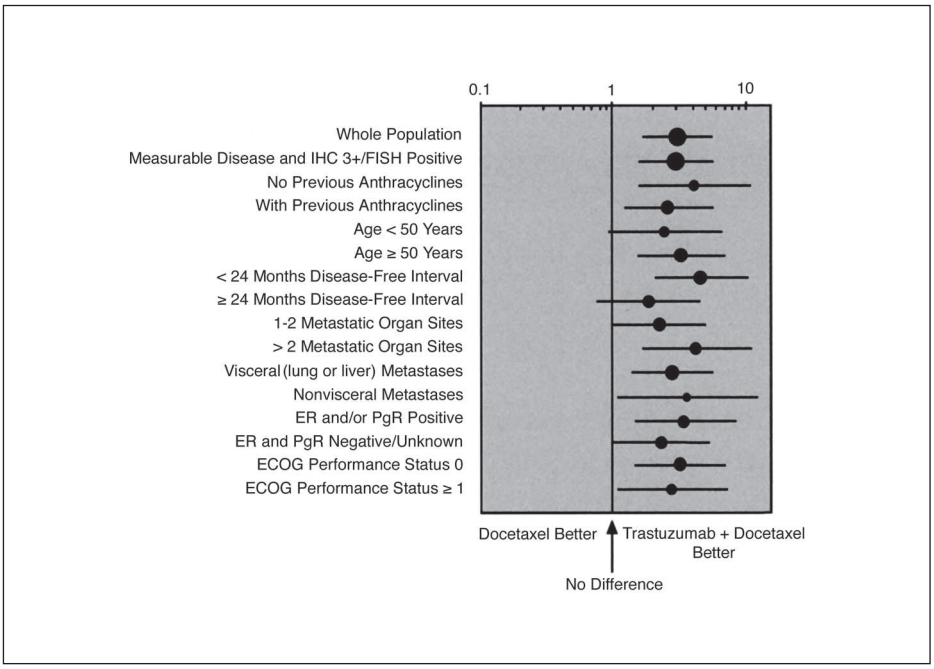

Fig 1. Subgroup analysis: Forest plot of odds ratios ± 95% CIs. IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ER, estrogen receptor; PgR, progesterone receptor; ECOG, Eastern Cooperative Oncology Group.

The majority of adverse events were mild to moderate in severity. Common nonhematologic events (reported in ≥ 20% of patients, regardless of whether the events were attributable to study treatment) were typical of chemotherapy-related toxicity (eg, alopecia, nausea, and vomiting; Table 3). The incidence of adverse events typically associated with trastuzumab (eg, pyrexia) was seen, as expected, in the combination arm. In addition, there was a slightly higher incidence of typical docetaxel-related adverse events (eg, stomatitis, paraesthesia) in the combination arm and also of events not considered typical for either trastuzumab or docetaxel (eg, headache). Overall, there was a higher incidence of grade 3 (67% *v* 55%) and 4 (34% *v* 23%) adverse events (all causes) in the combination arm compared with the docetaxel-alone arm. However, most of the imbalances noted were due to a higher incidence of grade 1 and 2 toxicities. There were three serious infusion-related reactions: one in the docetaxel-alone arm and two in the combination arm. Of the latter two events, one was related to docetaxel and one to trastuzumab. Overall, fewer patients in the combination arm discontinued treatment due to adverse events compared with those in the docetaxel-alone arm (nine *v* 20 patients, respectively). In the docetaxel-alone arm, 29 patients experienced 42 SAEs; in the combination arm, 38 patients experienced 64 SAEs.

Hematologic toxicity. There was a higher incidence of grade 3/4 leukopenia and neutropenia (20% *v* 15%, and 32% *v* 22%, respectively) in the combination arm compared with the docetaxel-alone arm (Table 4). The incidence of febrile

Table 2. Summary of Efficacy Between the Two Treatment Arms

Outcome	Trastuzumab + Docetaxel (n = 92)	Docetaxel Alone (n = 94)	*P*
ORR, %	61	34	.0002
CR, %	7	2	
PR, %	54	32	
SD, %	27	44	
DR, median, months	11.7	5.7	.009
TTP, median, months	11.7	6.1	.0001
OS, median, months*	31.2	22.7	.0325

Abbreviations: ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; DR, duration of response; TTP, time to progression; OS, overall survival.
*Kaplan-Meier estimate.

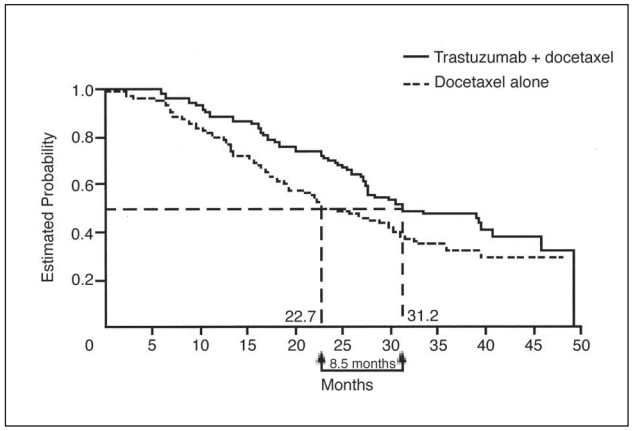

Fig 2. Comparison of estimated overall survival between trastuzumab plus docetaxel and docetaxel-alone arms (Kaplan-Meier plots).

Table 3. Incidence of Nonhematologic Adverse Events (% of patients)

Adverse Event*	Total		Grade 3/4	
	Trastuzumab + Docetaxel (n = 92)	Docetaxel Alone (n = 94)	Trastuzumab + Docetaxel (n = 92)	Docetaxel Alone (n = 94)
Alopecia	67	54	10	6
Asthenia	45	41	10	6
Nausea	45	41	0	1
Diarrhea	43	36	5	2
Peripheral edema	40	35	1	2
Paraesthesia	32	21	0	2
Vomiting	29	22	3	2
Pyrexia	30	15	1	1
Constipation	27	23	2	0
Myalgia	27	26	3	3
Arthralgia	27	20	4	0
Rash	24	12	1	0
Fatigue	24	21	3	3
Mucosal inflammation	23	22	2	4
Erythema	23	11	1	0
Anorexia	22	13	2	0
Headache	21	18	5	1
Increased lacrimation	21	10	1	0
Epistaxis	20	5	0	0

*Reported in ≥ 20% of patients in at least one treatment arm.

neutropenia was 23% in the combination arm (95% CI, 14.7% to 32.8%) compared with 17% in the docetaxel-alone arm (95% CI, 10.0% to 26.2%; Table 4). All patients experiencing febrile neutropenia received empiric antibiotics, with granulocyte colony-stimulating factor administered to four patients in the combination arm and three patients in the docetaxel-alone arm. There were two drug-related deaths as a result of septicemia in the docetaxel arm. All other episodes resolved within 1 week and, in most cases, without recurrence after a dose reduction of docetaxel. Anemia experienced was generally mild. There was an increased incidence in grade 1/2 anemia in the combination arm compared with the docetaxel-alone arm (80% *v* 66%). The incidence of grade 3 anemia was 1% *v* 1%, and no grade 4 anemia was recorded.

Cardiac safety. Slightly more patients experienced decreases in LVEF in the combination arm compared with the docetaxel-alone arm (Table 5): asymptomatic declines in LVEF of 15 or more percentage points occurred in 17% *v* 8% of patients, respectively. Twelve of the 15 patients in the combination arm who experienced a decrease in LVEF had received prior adjuvant anthracycline therapy.

Two patients experienced symptomatic congestive heart failure (CHF); both patients received docetaxel and trastuzumab. These patients had received prior adjuvant anthracycline therapy (cumulative dose 300 mg/m^2 doxorubicin in both patients). The first of these patients entered the trial with a baseline LVEF of 60%. The patient had exertional dyspnea and a decrease in LVEF to 45% during cycle six of treatment and peripheral edema during the following cycle. Two

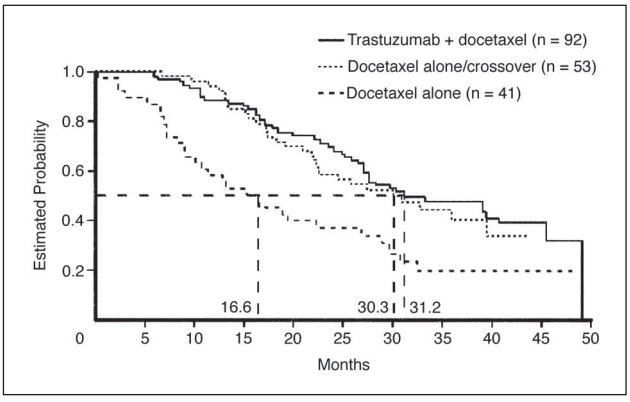

Fig 3. Comparison of estimated overall survival in patients who received trastuzumab and docetaxel first-line treatment versus those who crossed over to receive trastuzumab after progressing on docetaxel alone versus patients who received docetaxel only (Kaplan-Meier plots).

Table 4. Hematologic Toxicity (grade 3/4; % of patients)

Toxicity	Trastuzumab + Docetaxel (n = 92)	Docetaxel Alone (n = 94)
Anemia	1	1
Thrombocytopenia	0	0
Leukopenia	20	15
Neutropenia	32	22
Febrile neutropenia/neutropenic sepsis	23	17

Table 5. Changes in LVEF From Baseline: Worst Value Up to Cycle 6 and Overall (% of patients)

LVEF Worst Value	Up to Cycle 6		Overall*	
	Trastuzumab + Docetaxel (n = 83)	Docetaxel Alone (n = 71)	Trastuzumab + Docetaxel (n = 86)	Docetaxel Alone (n = 76)
Increase or no change	41	41	20	33
Absolute decrease < 15%	48	54	63	60
Absolute decrease ≥ 15%	11	6	17	8
Absolute value < 40%	1	0	1	0

Abbreviation: LVEF, left ventricular ejection fraction.
*LVEF monitoring ceased in patients receiving docetaxel alone after completion of therapy. However, LVEF monitoring continued throughout trastuzumab treatment in the combination arm. The number of LVEF assessments is therefore markedly different in the two arms after cycle 6.

weeks into cycle 7, the dyspnea and peripheral edema were still present and her LVEF had decreased to 40%. The investigator therefore decided to discontinue trastuzumab. Four weeks later, the patient was admitted to the hospital in a coma and died the following day. Death was attributed to progressive metastatic disease. The investigator could not rule out trastuzumab-related cardiotoxicity.

The second patient, who had previously received adjuvant doxorubicin, received six cycles of docetaxel and 97 weekly infusions of trastuzumab, with no evidence of cardiac dysfunction during trastuzumab therapy. One month after discontinuing trastuzumab because of progressive disease, she entered a clinical trial of an investigational anthracycline. Four months later, she experienced fatal biventricular failure, which was considered by the investigator to be related to the novel anthracycline.

DISCUSSION

This randomized, open-label trial compared the efficacy and safety of trastuzumab plus docetaxel versus docetaxel alone in women with HER2-positive MBC. The combination of trastuzumab with docetaxel was superior to docetaxel alone in all clinical efficacy parameters investigated.

Fifty-six patients (61%) achieved a CR or PR in the combination arm compared with 32 patients (34%) in the docetaxel-alone arm ($P = .0002$). The sensitivity analysis showed that the statistically significant difference between the arms remained whether the seven patients in the docetaxel-alone arm not assessable for response (because of early discontinuation of study medication) were counted as responders or excluded from the ITT population. A subgroup analysis of response rates showed a consistent superiority of the combination arm over the docetaxel-alone arm for all baseline characteristics assessed (Fig 1). Apart from more patients with ER- or PgR-positive disease in the docetaxel-alone arm compared with the combination arm (56% *v* 41%) and more patients in the combination arm who had received prior (neo)adjuvant anthracyclines (64% *v* 55%), the arms were well balanced and there is no evidence for any selection bias.

All other efficacy parameters were also improved by the addition of trastuzumab to docetaxel. These included DR (median, 11.7 *v* 5.7 months; $P = .009$), TTP (median, 11.7 *v* 6.1 months; $P = .0001$), and OS (median, 31.2 *v* 22.7 months; $P = .0325$). Importantly, the improvement in survival was seen even though approximately 50% of patients in the docetaxel-alone arm crossed over to receive trastuzumab, which could be expected to dilute any survival benefit conferred by trastuzumab administered as first-line therapy.

Survival was longest for the group who received trastuzumab and docetaxel concomitantly from the start of treatment (median OS, 31.2 months). Patients in the docetaxel-alone arm known to have received trastuzumab after docetaxel appeared to survive longer than those who did not receive subsequent trastuzumab (median OS, 30.3 *v* 16.6 months, respectively). It is possible that earlier treatment with trastuzumab led to the improvement in survival. However, there are possible confounding factors such as poor performance status influencing both the decision to cross the patient over to trastuzumab and the progress of the disease. This analysis was unplanned and explorative, and therefore needs to be interpreted with caution.

The results from this trial of trastuzumab and docetaxel are in line with the findings of the combination pivotal trial (H0648g) of first-line paclitaxel with or without trastuzumab in HER2-positive MBC.[6,7] In the H0648g trial, ORR increased from 17% to 49% with the addition of trastuzumab to paclitaxel in patients with IHC 3+ MBC. In addition, TTP increased from 3.0 to 7.1 months and OS increased from 17.9 to 24.8 months. The improvement in survival was seen even though 72% of patients randomly assigned to paclitaxel alone crossed over to receive trastuzumab at progression. Although there were some differences between the patient populations in the two trials (in particular, all patients in the paclitaxel plus trastuzumab arm of study H0648g had received prior adjuvant anthracycline therapy), the results are nonetheless very similar

between the studies. Most notably, in both trials, patients treated with trastuzumab plus a taxane had a median survival of between 2 and 2.5 years. The concordant results in these two randomized trials provide strong evidence supporting the use of trastuzumab plus a taxane as first-line therapy for women with HER2-positive MBC.

The efficacy gains are significant and achieved without significant increase of toxicity. Overall, the safety profiles of the two arms in trial M77001 were similar. Several of the nonhematologic toxicities commonly seen with docetaxel, such as alopecia and paraesthesia, occurred more frequently in the combination arm, suggesting additivity or even a degree of exacerbation. In the combination arm, there was a greater incidence of infusion-related reactions that can occur with initial doses of trastuzumab. However, it is noteworthy that several of the most troublesome adverse effects associated with chemotherapy, such as nausea, vomiting, and mucositis, were not markedly different between the arms and were generally limited to NCI CTC grades 1 and 2. Grade 3 to 4 toxicities were uncommon and showed little difference between the two groups.

There is an indication of a slight exacerbation by trastuzumab of some docetaxel-related hematologic toxicities, which corroborates a previous report.[22] Episodes of febrile neutropenia were generally manageable, and usually resolved rapidly with standard medical interventions. Furthermore, although there were two deaths as a result of septicemia in the docetaxel-alone arm, none were reported in the combination arm. Although the incidence of adverse events overall was greater in the combination arm, discontinuations because of adverse events were actually more common in the docetaxel-alone arm (9% *v* 20%). This probably reflects the better clinical outcome of patients receiving trastuzumab with docetaxel and the greater willingness of both patients and physicians to persevere in the face of toxicities when disease is improving.

Cardiac dysfunction had been a concern in the H0648g trial. A retrospective analysis showed the incidence of symptomatic heart failure to be approximately 9% among patients receiving trastuzumab plus paclitaxel.[23] Subsequent trials of trastuzumab that have included cardiovascular eligibility criteria and prospective cardiac monitoring have shown an incidence of CHF of less than 4%.[19,24-29] In an analysis of pooled cardiac data from six trastuzumab phase II/III trials (n = 629; 418 with trastuzumab, 211 controls), including trial M77001, the incidence of CHF in trastuzumab-treated patients was only 2.7% (11 of 418).[30] Two of 92 patients (2%) receiving trastuzumab plus docetaxel in trial M77001 developed symptomatic heart failure. Both patients had received prior adjuvant anthracyclines. One patient developed CHF during the study. The other patient developed CHF 5 months after discontinuation of trastuzumab, and had received an investigational anthracycline only a month after completing trastuzumab, despite the recommended 24-week washout period between completing trastuzumab and commencing anthracycline therapy. These data suggest that treatment with trastuzumab in combination with docetaxel has manageable cardiac toxicity, the incidence of which is within the range expected for patients receiving trastuzumab plus chemotherapy in more recent clinical trials.

The results of the M77001 trial, which show a significant survival benefit for trastuzumab in combination with docetaxel, provide for an additional valuable first-line treatment option in routine clinical practice for patients with HER2-positive MBC. Other trials are taking the trastuzumab plus docetaxel combination forward, both in the metastatic and adjuvant settings. Randomized trials in patients with HER2-positive MBC are being performed to investigate the additional benefit of adding in a third drug, such as capecitabine (as in the ongoing MO16419 trial) or carboplatin (as in the BCIRG 007 trial, which has recently completed recruitment). Four large adjuvant trials of trastuzumab in patients with HER2-positive breast cancer are currently being conducted: the Herceptin Adjuvant Trial (HERA), National Surgical Adjuvant Breast and Bowel (NSABP) Project, Intergroup, and Breast Cancer International Research Group (BCIRG) 006 trials. Whereas trastuzumab is administered as monotherapy in the HERA trial after the completion of standard adjuvant chemotherapy, the NSABP and Intergroup trials investigate trastuzumab administered either concurrently or sequentially with paclitaxel, after anthracycline plus cyclophosphamide chemotherapy. In the BCIRG 006 trial, docetaxel is administered either on its own or concurrently with trastuzumab, after AC chemotherapy; a third arm of this trial is examining the combination of docetaxel, trastuzumab, and carboplatin (analogous to BCIRG 007). All of these trials have passed their per-protocol scheduled interim safety analyses. The final results of these adjuvant trials are awaited with great interest.

In the meantime, recent results of a randomized trial of trastuzumab administered as neoadjuvant therapy in patients with HER2-positive operable breast cancer showed that the addition of trastuzumab provided a significant increase in the pathologic CR rate in combination with paclitaxel and fluorouracil, epirubicin, and cyclophosphamide compared with chemotherapy alone.[31]

In summary, the results of the M77001 trial, together with the H0648g trial (trastuzumab in combination with paclitaxel) provide strong evidence that the combination of trastuzumab with a taxane is efficacious and well tolerated as first-line therapy for women with HER2-positive MBC, offering a significant survival benefit as well as a higher rate and longer duration of responses, compared with a taxane alone. In addition, the benefit shown for trastuzumab in this trial supports ongoing investigations of trastuzumab in

the neoadjuvant and adjuvant treatment of patients with HER2-positive breast cancer.

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The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Michel Marty, IGR; Ray Snyder, Aventis; Kenneth O'Byrne, Roche. Performed contract work within the last 2 years: Michel Marty, IGR; Ray Snyder, Aventis. Served as an officer or member of the Board of a company: Ray Snyder, Aventis. Received more than $2,000 a year from a company for either of the last 2 years: Kenneth O'Byrne, Roche; Carol Ward, Roche; Karen Mayne, Roche.

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