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ORIGINAL REPORT

Phase III Randomized Study Comparing Docetaxel Plus Trastuzumab With Vinorelbine Plus Trastuzumab As First-Line Therapy of Metastatic or Locally Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: The HERNATA Study

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ABSTRACT

Purpose
To evaluate docetaxel or vinorelbine, both with trastuzumab, as first-line therapy of human epidermal growth factor receptor 2–positive advanced breast cancer.

Patients and Methods
Patients naive to chemotherapy for advanced disease were randomly assigned to docetaxel 100 mg/m^2 day 1 or vinorelbine 30 to 35 mg/m^2 on days 1 and 8, both combined with trastuzumab (8-mg/kg loading dose and 6-mg/kg maintenance dose) on day 1 every 3 weeks. The primary end point was time to progression (TTP).

Results
A total of 143 patients were randomly allocated to docetaxel, and 141 patients were assigned to vinorelbine. The median TTP for docetaxel and vinorelbine respectively was 12.4 months versus 15.3 months (hazard ratio [HR] = 0.94; 95% CI, 0.71 to 1.25; $P = .67$), median overall survival was 35.7 months versus 38.8 months (HR = 1.01; 95% CI, 0.71 to 1.42; $P = .98$), and the 1-year survival rate was 88% in both arms. Median time to treatment failure for study chemotherapy was 5.6 months versus 7.7 months (HR = 0.50; 95% CI, 0.38 to 0.64; $P < .0001$). The investigator-assessed overall response rate among 241 patients with measurable disease were 59.3% in both arms. More patients in the docetaxel arm discontinued therapy due to toxicity ($P < .001$). Significantly more treatment-related grade 3 to 4 febrile neutropenia (36.0% *v* 10.1%), leucopenia (40.3% *v* 21.0%), infection 25.1% *v* 13.0%), fever (4.3% *v* 0%), neuropathy (30.9% *v* 3.6%), nail changes (7.9% *v* 0.7%), and edema (6.5% *v* 0%) were reported with docetaxel.

Conclusion
The study failed to demonstrate superiority of any drug in terms of efficacy, but the vinorelbine combination had significantly fewer adverse effects and should be considered as an alternative first-line option.

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INTRODUCTION

Breast cancer is the most common malignant disease and among the most frequent causes of cancer mortality in females worldwide.[1,2] Most cases of breast cancer are early stage and operable at presentation. However, a fraction of cases will, after a variable disease-free interval, recur with distant metastases. Metastatic breast cancer (MBC) is conventionally considered to be incurable, with median survival estimates to be in the range of 3 years. In 15% to 20% of individuals with breast cancer, the tumors are overexpressing the c-erb-2 receptor (human epidermal growth factor receptor 2 [HER2]–positive breast cancer). HER2-positive breast cancer is characterized by an aggressive course, with shortened disease-free interval and high mortality rate.[3] Trastuzumab is a monoclonal antibody targeting the external domain of the c-erb-2 receptor. In first-line treatment of HER2-positive MBC, randomized trials have demonstrated that trastuzumab when combined with paclitaxel or docetaxel significantly improves median time to progression (TTP; with 3.9 and 5.6 months, respectively) and overall survival (OS; with 3.7 and 8.5 months, respectively).[4,5] Trastuzumab in combination

with a taxane as first-line therapy for HER2-positive MBC is now considered as a standard of care in many institutions, and there is retrospective evidence to suggest that the introduction of trastuzumab in this setting has markedly improved the prognosis.[6] However, toxicities from taxane-containing chemotherapy, especially when administered every 3 weeks, are often serious, causing dose reductions and treatment discontinuations.[7]

Vinorelbine is a vinca alkaloid chemotherapeutic drug that, in preclinical studies in several HER2-positive breast cancer cell lines, has been demonstrated to act synergistically with trastuzumab.[8] Several phase II trials with the combination of vinorelbine and trastuzumab as first-line treatment in HER2-positive breast cancer have demonstrated high rates of response (48% to 86%) with manageable toxicity.[9]

In the present Herceptin Plus Navelbine or Taxotere (HERNATA) study, patients with HER2-positive MBC or locally advanced breast cancer (LABC) were randomly assigned to receive either docetaxel or vinorelbine, both in combination with trastuzumab, as first-line treatment. The primary objective was to compare TTP between treatments. Secondary objectives included OS, 1-year survival, rate of response (RR), time to treatment failure (TTF), and toxicity and tolerability.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients were 18 to 75 years of age with MBC or LABC verified histologically or cytologically and HER2-positive status assessed locally by immunohistochemistry (3+) or fluorescent in situ hybridization positivity on the primary cancer or from a biopsy of a metastatic lesion. The patients had to have measurable or nonmeasurable disease; performance status ≤ 2 according to WHO; adequate bone marrow, liver, renal, and cardiac function with normal left ventricular ejection fraction as defined by each institution; and an estimated life expectancy of more than 12 weeks. Chemotherapy and HER2-targeted treatment was allowed as (neo-) adjuvant therapy (for taxanes, vinorelbine, and trastuzumab $>$ 12 months before), but not for treatment of metastatic or locally advanced disease. Previous hormonal therapy was allowed for both early-stage and advanced disease. Ineligibility criteria included brain metastasis, dyspnea, second primary malignancy, and serious concomitant illness.

Study Design

The study was conducted in accordance with the Declaration of Helsinki. The patients received oral and written information, and a written informed consent was obtained from all patients. The study was approved by the ethical committees with jurisdiction for the participating institutions.

The HERNATA study was a randomized, multicenter, phase III trial conducted at institutions in Denmark, Sweden, and Norway. Patients were, unstratified, randomly assigned centrally by the Danish Breast Cancer Cooperative Group Secretariat after confirmation of eligibility to receive either docetaxel 100 mg/m^2 intravenously (IV) over 60 minutes every 3 weeks or vinorelbine 30 mg/m^2 or 35 mg/m^2 (according to institutional predefined preference) IV as bolus injection days 1 and 8 every 3 weeks. Trastuzumab was administered before chemotherapy as an intravenous infusion over 90 minutes with 8 mg/kg in the first cycle and at subsequent cycles over 30 minutes with 6 mg/kg. In the first cycle, docetaxel was administered the day after trastuzumab. Pretreatment supportive medications including antiemetics were given according to institutional practice. Secondary antibiotic and granulocyte colony-stimulating factor support were allowed. Toxicity reporting used the National Cancer Institute Common Toxicity Criteria version 3.0. For docetaxel, in case of toxicity grade 3 to 4 (or for grade 2 neuropathy and fluid retention), treatment was to be delayed until toxicity improved to grade 1, followed by dose reduction to 75% and, if recurring, to 60%. In case neuropathy or fluid retention grade 3 occurred, treatment was to be discontinued. For vinorelbine, in case of toxicity grade 3 to 4, treatment was to be delayed until toxicity improved to grade 1, and then dose was to be reduced to 80%. In case of elevation of bilirubin more than 2$\times$ the upper limit of normal or transaminases more than 3$\times$ the upper limit of normal, the dose was reduced with 50%. No dose reduction was planned for trastuzumab. Continuation of trastuzumab despite decline of left ventricular ejection fraction (LVEF) was at the discretion of the physician. If one component of the treatment was discontinued, then the other component (chemotherapy or trastuzumab) could continue. Treatment duration was until progression, intolerable toxicity, or patient withdrawal. Treatment after discontinuation of study medication was at the discretion of the physician.

Study Evaluations

Prestudy evaluations ($\leq$ 14 days before random assignment) included medical history, physical examination, evaluation of performance status, ECG, chest x-ray, bone scan, ultrasound, computed tomography scan or magnetic resonance imaging scan of chest and abdomen, blood chemistries, blood counts, assessment of LVEF by echocardiography or multiple-gated acquisition scan, and tumor evaluation. Blood chemistries, blood counts, and evaluation of toxicity were repeated at each cycle. Physical examination, evaluation of performance status, and tumor evaluation using the baseline methods were repeated every third cycle. Assessment of LVEF was conducted at cycles 3 and 6 and then every sixth cycle. Assessments after progression (or after change of chemotherapy for any other reason) were run every 3 months and included vital status, disease status, delivered antineoplastic drug, and cardiac adverse effects with focus on congestive heart failure. TTP was measured from random assignment to date of documented progression with censoring for (for patients alive) at last visit date or at date of death. OS was calculated from date of random assignment to date of death with censoring for patients still alive at last visit date. TTF was defined as the time from date of random assignment to the date of the last study chemotherapy administration, with censoring for patients still on treatment. Note that this definition of TTF allows continued trastuzumab beyond TTF. Response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST) version 3.0 criteria modified to include ultrasound as eligible modality.

Statistical Methods

At the time of conception of the study, it was believed that the vinorelbine plus trastuzumab combination was inferior to docetaxel plus trastuzumab in terms of efficacy. Thus earlier studies had reported median TTF of 6.0 months for vinorelbine plus trastuzumab[10] compared with median TTP of 10.6 months with docetaxel plus trastuzumab.[11] However, because of the perceived favorable toxicity profile of vinorelbine plus trastuzumab, this combination had become popular at several of the participating institutions. If such a difference (hazard ratio [HR] = 1.77) was assumed, a sample size of 282 patients included over 3 years would result in a 90% power at 5% level of significance to reject the hypothesis of similar TTP.

All randomly assigned patients were analyzed for efficacy according to the intent-to-treat principle, and all who received at least one dose of study medication were evaluated for safety. Time-to-event end points (TTP, OS, and TTF) were estimated by the Kaplan-Meier method, and the therapy arms were compared using the log-rank test. Analyses of treatment effects were conducted unadjusted and adjusted for preselected covariates in multivariate Cox proportional hazards models. The multivariate models included age, recurrence-free interval, hormone receptor status, disease type (visceral *v* nonvisceral only), WHO performance status, stage of disease (locally advanced *v* metastatic), and previous adjuvant chemotherapy. The assumption of proportional hazards was assessed by Schoenfeld residuals.[12]

Exploratory analyses were done to assess whether treatment effects on TTP varied according to the levels of the seven preselected variables. The multivariate Cox proportional hazards model was extended by one interaction term at a time. The interaction terms were tested using the Wald test and results were given in a Forest plot.

RR was evaluated for patients with measurable disease. The overall response rate (ORR) was defined as a complete or partial response according to

RECIST criteria. Categorical valuables were compared using Fisher's exact test, and 95% two-sided CIs were constructed for all parameter estimates.

RESULTS

From May 2004 to August 2008, a total of 284 patients were enrolled at 27 institutions in Denmark, Sweden, and Norway. Baseline demographic and other variables were well balanced between the treatment groups (Table 1). Approximately half of the patients had received adjuvant chemotherapy. All but four of the patients were naive to taxanes, and all patients but one were naive to trastuzumab. At the time of analysis, with a potential follow-up time of 34 months, 150 patients had experienced disease progression and 29 patients were still receiving treatment with study chemotherapy (CONSORT diagram,

Table 1. Demographics and Clinical Characteristics of All Randomly Assigned Patients

Characteristic	Docetaxel + Trastuzumab		Vinorelbine + Trastuzumab		All Patients	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
No of patients randomly assigned	143		141		284	
Age						
Median	56		57		56	
Range	33-72		29-72		29-72	
Performance status						
0	94	65.7	96	68.1	190	66.9
1	38	26.6	36	25.5	74	26.1
2	9	6.3	9	6.4	18	6.3
Recurrence-free interval, months						
Median	35		38		36	
Range	0-197		0-214		0-214	
Stage of disease						
Locally advanced	4	2.8	7	5.0	11	3.9
Metastatic	139	97.2	134	95.0	273	96.1
Hormone receptor status						
Positive	76	53.1	85	60.3	161	56.7
Negative	64	44.8	55	39.0	119	41.9
Unknown	3	2.1	1	0.7	4	1.4
HER2 status						
IHC 3+	116	81.1	117	83.0	233	82.0
FISH+	51	35.7	49	34.8	100	35.2
Negative/unknown	2	1.4	2	1.4	4	1.4
Measurable disease	123	86.0	118	83.7	241	84.9
No. of metastatic sites						
1	31	21.0	32	22.7	63	22.2
2	36	25.2	46	32.6	82	28.9
≥ 3	77	53.8	63	44.7	140	49.3
Type of metastatic sites						
Visceral	86	60.1	88	62.4	174	61.3
Liver	58	40.6	59	41.8	117	41.2
Lung	43	30.1	51	36.2	94	33.1
Bone	64	44.8	64	45.4	128	45.1
Nonvisceral only	57	39.9	53	37.6	110	38.7
Prior therapy						
Chemotherapy, adjuvant	59	41.3	70	49.6	129	45.4
Anthracycline	49	34.3	58	41.1	107	37.7
Taxane	1	0.7	3	2.1	4	1.4
Hormonal therapy						
Adjuvant	56	39.2	54	38.3	110	38.7
Locally advanced/metastatic	17	11.9	24	17.0	41	14.4
Radiotherapy						
Adjuvant	78	54.5	72	51.1	150	52.8
Locally advanced/metastatic	18	12.6	16	11.3	34	12.0
Trastuzumab						
Adjuvant	1	0.7	0	0	1	0.4
LVEF, %						
Median	62		63		63	
Range	45-84		50-86		45-86	

Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; LVEF, left ventricular ejection fraction.

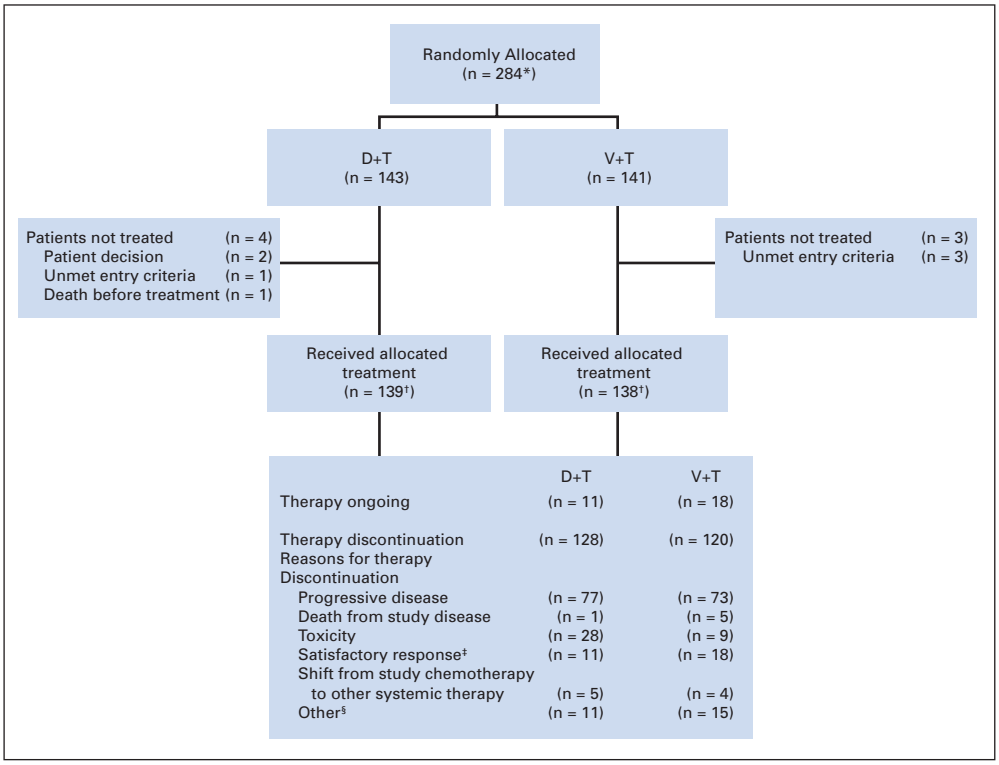

Fig 1. CONSORT flow diagram. (*) Patients included in the analysis of survival and secondary efficacy variables per intent-to-treat principle. (†) Patients who received at least one study drug dose and therefore were included in the safety analysis. (‡) Includes locally advanced disease given locoregional therapy. (§) Includes entry criteria not met, incorrect assessment of progression, clinical deterioration, and lost to follow-up. D, docetaxel; T, trastuzumab; V, vinorelbine.

Fig 1), whereas 133 patients had died, 123 as a result of breast cancer and 10 as a result of other causes. The number of events was, for docetaxel and vinorelbine, respectively, 96 versus 95 for TTP, 68 versus 65 for OS, and 127 versus 120 for TTF.

Treatment Delivered

A total of 1,148 cycles of docetaxel and 1,683 cycles of vinorelbine (30 mg/m^2, 1,032; 35 mg/m^2, 651) were administered. Dose reductions were more common with docetaxel, and dose delays were more common with vinorelbine (Table 2). Both reductions and delays were more common with vinorelbine at dose 35 mg/m^2 than with 30 mg/m^2. It should be noted that choice of vinorelbine dose was based on institutional practice and not on random assignment. Chemotherapy relative dose-intensity was lower with docetaxel (86%) than with vinorelbine (93%).

Efficacy

No difference was seen between the two treatment arms for primary or secondary efficacy end points, except for TTF for study chemotherapy. Median TTP was 12.4 months versus 15.3 months (HR = 0.94; 95% CI, 0.71 to 1.25; $P = .67$), and median OS was 35.7 months versus 38.8 months (HR = 1.01; 95% CI, 0.71 to 1.42; $P = .98$). The median TTF was shorter for docetaxel: 5.6 months compared with 7.7 months for vinorelbine (HR = 0.50; 95% CI, 0.38 to 0.64; $P = .0001$; Fig 2). The adjusted Cox proportional hazards model for TTF, TTP, and OS did not materially alter the conclusions (results not shown). Figure 3 shows that no heterogeneity between treatment arms with regard to preselected prognostic factors and TTP was observed, except for a significant interaction between hormone receptor status and chemotherapy regimen, with hormone receptor negative status favoring docetaxel and positive status favoring

Table 2. Chemotherapy Delivered

Characteristic	Docetaxel + Trastuzumab	Vinorelbine + Trastuzumab*		
		30 mg/m^2	35 mg/m^2	All
No. of patients who received therapy	139	91	47	138
No. of cycles delivered	1,148	1,032	651	1,683
No. of chemotherapy cycles				
Median	8	9	12	10.5
Range	0-26	2-42	3-27	2-42
Chemotherapy cycles delivered with reduced dose, %	45.7	17.3	36.0	24.7
Chemotherapy cycles delivered with delay, %	5.9	11.8	16.1	13.5
Relative dose-intensity, %	86	95	80	93

*Vinorelbine dose 30 mg/m^2 or 35 mg/m^2 was determined according to institutional practice.

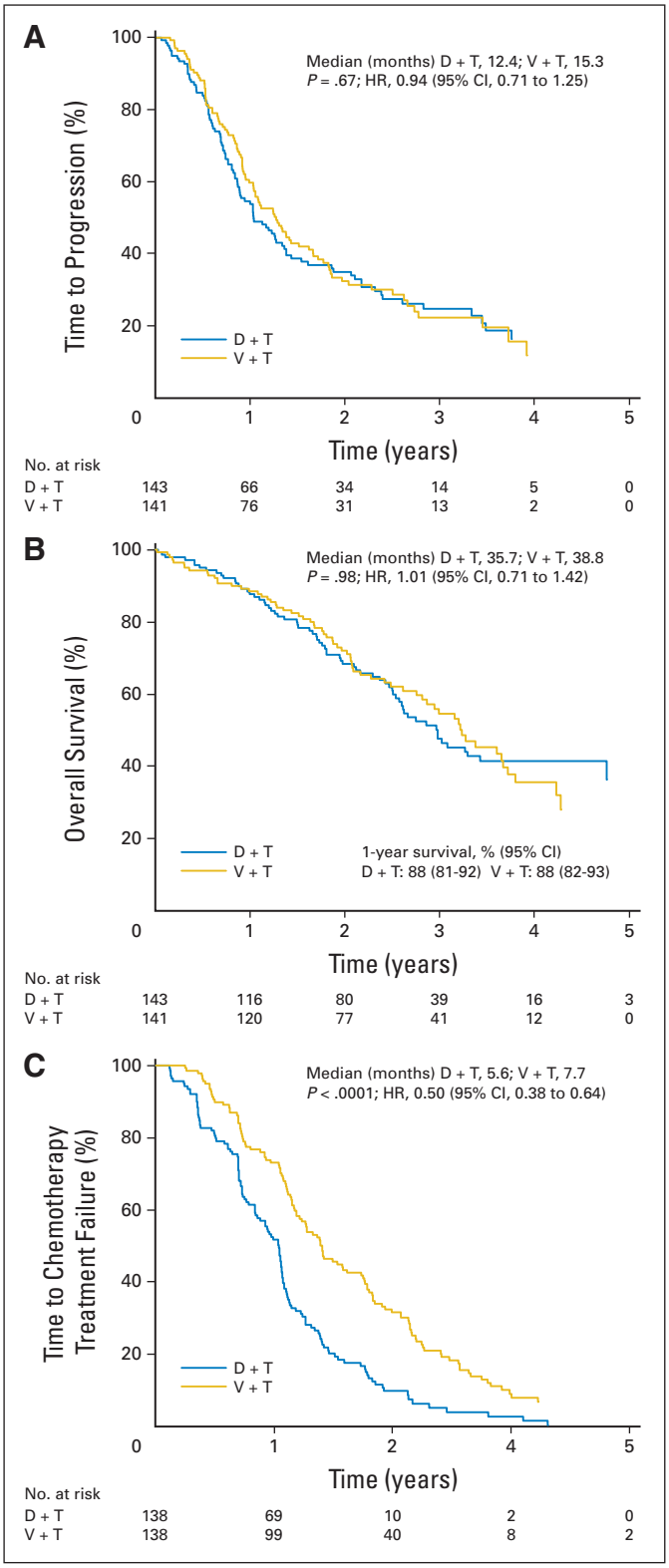

Fig 2. Kaplan-Meier curves for (A) time to progression, (B) overall survival, and (C) time to treatment failure for study chemotherapy. One-year survival for docetaxel plus trastuzumab (D+T), 88% (95% CI, 81% to 92%); vinorelbine plus trastuzumab (V+T), 88% (95% CI, 82% to 93%). HR, hazard ratio.

vinorelbine ($P = .03$). One-year survival rates for docetaxel and vinorelbine, respectively, were similar, at 88% (95% CI, 81% to 92%) and 88% (95% CI, 82% to 93%).

An unplanned exploratory analysis comparing the efficacy variables in patients given vinorelbine 30 mg/m^2 or 35 mg/m^2 (based on institutional preference, not random assignment) did not show any significant difference (results not shown).

RR among patients with measurable disease did not differ between docetaxel (n = 123) and vinorelbine (n = 118): complete response, 16 (13.0%) versus 13 (11.0%); partial response, 57 (46.3%) versus 57 (48.3%); stable disease, 20 (16.2%) versus 19 (16.1%); progressive disease, 9 (7.3%) versus 6 (5.1%); and not evaluable, 21 (17.0%) versus 23 (19.5%). Overall response rate (complete response plus partial response) was 73 (59.3%) versus 70 (59.3%; $P = 1.00$).

Toxicity

Table 3 depicts drug-related grade 2 to 4 toxicities observed, with grade 3 to 4 in more than 3% of patients per treatment arm. In general, toxicity was more common in the docetaxel arm compared with the vinorelbine arm. More patients had grade 3 to 4 toxicities with docetaxel than with vinorelbine (81% *v* 51%; $P < .0001$), and hematologic toxicity was more pronounced with docetaxel, with rates of febrile neutropenia of 37.2% versus 10.8% ($P < .0001$). One patient in the docetaxel arm died from septicemia subsequent to the first chemotherapy cycle. Significantly more grade 3 to 4 toxicities were seen for docetaxel than for vinorelbine with regard to leucopenia, febrile neutropenia, infections, fever, edema, nail changes, and sensory neuropathy. Treatment discontinuation owing to toxicity from study chemotherapy was more frequent with docetaxel (20.1%) than with vinorelbine (6.5%; Fig 1; $P < .001$).

Declines of LVEF were observed for docetaxel and vinorelbine, respectively, 1% to 14% from baseline in 45% versus 42%, more than 14% from baseline in 7.2% versus 10.9% ($P = .40$), and to a decline of LVEF less than 40% in 0.7% versus 3.6% ($P = .21$) of the safety population. One patient in the vinorelbine arm with severe pulmonary infection died as a result of severe congestive heart failure. She had not received prior anthracycline or mediastinal radiation. The treating physician did not consider the cardiac condition to be related to trastuzumab or vinorelbine.

Poststudy Medication

Two thirds of patients in both treatment arms received another chemotherapy after discontinuation of study chemotherapy (Table 4). Similar proportions received one, two, or more lines of poststudy chemotherapy. Slightly more patients in the docetaxel arm crossed over to receive vinorelbine than from the vinorelbine arm to receive docetaxel. More than a third of the patients in both arms received capecitabine. Notably, two thirds of patients in both arms received trastuzumab after discontinuation of study chemotherapy for any reason, including progressive disease.

DISCUSSION

In the HERNATA trial, we compared efficacy and tolerability of trastuzumab combined with either docetaxel or vinorelbine as first-line

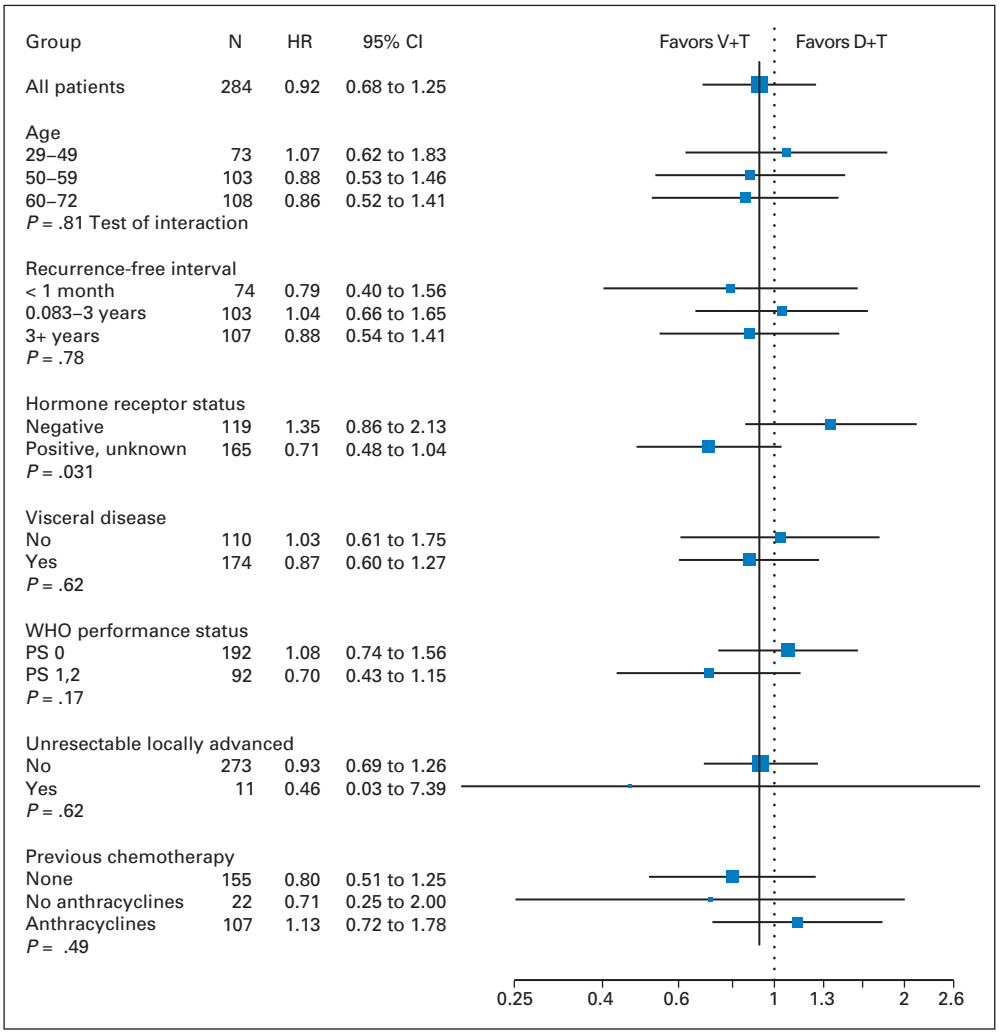

Fig 3. Forest plot of hazard ratios (HR) with 95% CIs for time to progression for preselected prognostic factors. V+T, vinorelbine plus trastuzumab; D+T, docetaxel plus trastuzumab; PS, performance score.

treatment of HER2-positive MBC or LABC. At the time of conception of the HERNATA study, it was hypothesized that docetaxel was superior to vinorelbine in terms of efficacy. However, we did not find any differences with HR for TTP of 0.94, HR for OS 1.01, 1-year survival rate of 88%, and overall RR of 59.3% in both arms. It should, however, be noted that the study was not dimensioned to demonstrate noninferiority, and correspondingly the CIs are wide. The observed median TTP (12.4 *v* 15.5 months), OS (median 35.7 *v* 38.8. months), and RR (59.3%) are consistent with findings from other studies with docetaxel and trastuzumab in first-line treatment of HER2-positive MBC.[5,13-15] Subgroup analysis showed a significant interaction between hormone receptor status and treatment arm, suggesting hormone receptor negativity to be a marker for sensitivity to docetaxel and/or hormone receptor positivity to be a marker for sensitivity to vinorelbine. To our knowledge, hormone receptor status has not been significantly linked to sensitivity to docetaxel or vinorelbine (eg,[16-19]), and the observation may represent a by-chance finding. TTF for study chemotherapy was significantly shorter with docetaxel (5.6 months) than with vinorelbine (7.7 months), indicating that patients stayed longer on vinorelbine than on docetaxel. This might be due to more patients on docetaxel discontinuing chemotherapy because of a satisfactory treatment result. However, it turned out that significantly more patients discontinued docetaxel than vinorelbine because of toxicity, whereas therapy discontinuation due to progression was similar (Fig 1). Consistent with this, grade 3 to 4 toxicity occurred significantly more frequent with docetaxel, including febrile neutropenia, leucopenia, infection, fever, sensory neuropathy, nail changes, and edema. The frequency of these grade 3 to 4 toxicities related to docetaxel and trastuzumab is consistent with findings from other randomized studies,[13-15] except that the frequency of febrile neutropenia among patients receiving docetaxel was relatively high. Use of secondary granulocyte colony-stimulating factor support was allowed, but was only used sporadically.

After the study, 53.3% of patient assigned to vinorelbine received taxane-containing chemotherapy, whereas 47.7% of docetaxel patients received vinorelbine (Table 4). The extent of chemotherapy lines received after the study was similar. Two thirds of patients received trastuzumab after discontinuation of study chemotherapy, indicating that trastuzumab therapy beyond progression on trastuzumab may have become part of standard of care in many of the participating institutions.

The present study is the fifth reported randomized trial exploring the optimal chemotherapy regimen combined with trastuzumab in HER2-positive MBC. Addition of carboplatin to

Table 3. Incidence of Drug-Related Toxicities Grade 2 to 4 Observed With Grade 3 to 4 in More Than 3% of Patients in Any Treatment Arm

Toxicity	% of Patients						*P* (grade 3 + 4, docetaxel *v* vinorelbine)
	Docetaxel + Trastuzumab (n = 139)			Vinorelbine + Trastuzumab (n = 138)			
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	
Hematologic							
Leucopenia	7.2	25.2	15.1	30.4	12.3	8.7	< .001
Neutropenia	2.9	6.5	37.4	2.9	26.1	15.4	.81
Febrile neutropenia	—	35.2	2.2	—	10.1	0.7	< .001
Nonhematologic							
Nausea	19.4	3.6	0	15.2	2.2	0	.72
Infection	23.0	23.0	0.7	21.0	11.6	1.4	.006
Pain	41.7	17.3	0	23.9	17.4	0.7	.55
Fatigue	41.7	11.5	1.4	34.1	6.5	1.4	.30
Diarrhea	17.3	8.6	0	8.0	3.6	0	.11
Neuropathy, motor	11.5	4.3	0	2.9	4.3	0	.75
Neuropathy, sensory	18.7	30.9	0	4.3	3.6	0	< .001
Edema	25.9	5.8	0	3.6	0	0	.003
Dyspnea	11.5	4.3	1.4	9.4	1.4	1.4	.54
Fever	13.7	3.6	0.7	11.6	0	0	.03
Nail changes	29.5	7.9	0	1.4	0.7	0	.005

paclitaxel plus trastuzumab[20] and addition of capecitabine to docetaxel plus trastuzumab[13] significantly increased progression-free survival, whereas addition of carboplatin to docetaxel plus trastuzumab resulted in similar TTP.[14] No survival advantage was seen in any study. In general, grade 3 to 4 toxicity was more frequent with the triplet combinations. One study comparing docetaxel or paclitaxel with vinorelbine, both combined with trastuzumab, closed prematurely because of slow accrual. Among only 81 eligible patients, no significant difference was observed with regard to RR, TTP, and TTF.[15] These results, together with the results from the present study, may imply that the choice of first-line chemotherapy drug in combination with trastuzumab may not be important as concerns regarding treatment efficacy, but it certainly is important in terms of toxicity.

In summary, the results from this randomized phase III trial of first-line therapy in HER2-positive MBC or LABC failed to demonstrate superiority in terms of efficacy of docetaxel plus trastuzumab compared with vinorelbine plus trastuzumab. However, toxicity was much more pronounced with docetaxel, and thus vinorelbine plus trastuzumab should be considered as an alternative first-line option with a favorable risk/benefit balance.

Table 4. Summary of Poststudy Therapy

Characteristic	Docetaxel + Trastuzumab		Vinorelbine + Trastuzumab	
	No.	%	No.	%
No. of patients*	127		118	
Extent of chemotherapy, lines				
1	36	27.3	37	30.3
2	23	17.4	15	12.3
> 2	30	22.7	29	23.8
Cross-over to vinorelbine/docetaxel	63	47.7	45	36.9
Most frequent other chemotherapy drugs				
Capecitabine	50	37.9	43	35.2
Anthracycline	26	19.7	22	18.0
Paclitaxel	14	10.6	20	16.4
Gemcitabine	8	6.1	5	4.1
HER2-targeted therapy				
Trastuzumab	84	63.6	76	62.3
Lapatinib	15	11.4	10	8.2
Hormonal therapy	43	32.6	35	28.7

Abbreviation: HER2, human epidermal growth factor receptor 2.
*All randomly assigned patients except patients still receiving study chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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