Phase II Study of a Triple Combination of Oral Vinorelbine, Capecitabine and Trastuzumab as First-line Treatment in HER2-positive Metastatic Breast Cancer

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Abstract. *Chemotherapy plus trastuzumab is the standard first-line treatment for Human Epidermal Receptor 2-positive (HER2-positive) metastatic breast cancer. The aim of this international phase II trial was to determine the efficacy and safety profile of an oral chemotherapy doublet, oral vinorelbine plus capecitabine, and trastuzumab in this setting. Patients and Methods: In this single-arm, multicenter, open-label phase II study, in the first-line metastatic setting, patients received 3-weekly cycles of oral vinorelbine at 80 mg/m^2 (first cycle dose 60 mg/m^2) day 1 and day 8, plus capecitabine at 1000 (750 if ≥65 years) mg/m^2 twice daily on days 1-14, plus trastuzumab at 4 mg/kg intravenously (i.v.) on day 1 (loading dose) then 2 mg/kg i.v. weekly thereafter. Treatment was continued until progression or unacceptable toxicity. Results: Fifty patients with a median age of 53.5 years were enrolled. Most (82%) had visceral involvement and 34% had more than two metastatic sites. The objective response rate (RECIST 1.0) in 44 evaluable patients was 77% [95% Confidence Interval (CI)=62-89%], including complete response in 21%. The clinical benefit rate (response or stable disease for ≥6 months) was 93% [95% CI=81-99%]. Median duration of response was 13.3 [95% CI=9.8-15.7] months, median progression-free survival was 12.8 [95% CI=10.8-16.9] months and median overall survival was 47.0 [95% CI=30.5-64.3] months. Median number of cycles was 10 (range 1-81). The majority of patients (72%) received more than 18 weeks and 32% more than 48 weeks of treatment. The most frequent treatment-related grade 3/4 adverse events were neutropenia (71%), hand-foot syndrome (20%) and diarrhea (16%). A low-rate of grade 2 alopecia was observed (14%). Conclusion: The triple combination of oral vinorelbine, capecitabine and trastuzumab is highly active in terms of response rate, progression-free survival and overall survival, with a manageable toxicity profile.*

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Chemotherapy given in combination with trastuzumab, a humanized monoclonal antibody directed against Human Epidermal Receptor-2, represents the standard first-line approach for patients who have HER2-positive metastatic breast cancer. In this setting, the inclusion of trastuzumab improved response rates, time-to-progression and overall

survival in two randomized trials (1). In the initial trials, trastuzumab was combined with a taxane, but more recent studies have suggested that other chemotherapeutic agents, such as vinorelbine, yield similar results (2). The vinorelbine plus trastuzumab combination is among the recommended options as first-line treatment for metastatic disease (3, 4). Vinorelbine, a semisynthetic third-generation vinca alkaloid, has demonstrated a consistent synergistic interaction with trastuzumab in pre-clinical models (5). A great number of phase II trials showed consistent efficacy and good tolerability of this combination (6, 7). Moreover, a recent randomized phase III trial of first-line therapy comparing docetaxel plus trastuzumab to vinorelbine plus trastuzumab showed similar efficacy in both arms, and more pronounced toxicity with docetaxel. This suggests that vinorelbine plus trastuzumab should be considered as an alternative first-line option with a favourable risk/benefit balance (8). Several studies evaluating the combination of oral vinorelbine with trastuzumab reported high activity (responses rates between 61% and 84% and progression-free survival between 9 and 12 months) with an excellent tolerance profile (9-12). Capecitabine is an oral prodrug of the antimetabolite fluorouracil that is frequently used in patients with metastatic breast cancer and provides consistent response rates with acceptable toxicity (13). Additive activity of the combination of trastuzumab with capecitabine was demonstrated in animal models of human breast cancer (14). Several phase II studies showed that this combination is clinically active, especially in heavily pre-treated patients (15-17). The different modes of action of vinorelbine and capecitabine, preclinical demonstration of synergism of these two agents, and the non-overlapping toxicity profile underscore the rationale for evaluating this combination in the first-line metastatic setting (18). Furthermore, the oral formulation of vinorelbine with capecitabine produced comparable response rates to intravenous vinorelbine in combination with other cytotoxics, suggesting that the oral doublet may be an alternative to the use of taxane-based combinations (19-22). We now report on the final results of the activity and safety of the triple combination of oral vinorelbine, capecitabine and trastuzumab as first-line therapy for patients with HER2-positive metastatic breast cancer.

Patients and Methods

Study design. This was a multicenter, open-label, phase II trial. The primary endpoint of the study was overall response rate. Secondary objectives included safety evaluation, clinical benefit (=complete response + partial response + stable disease of at least 6 months), duration of response, progression-free survival, time-to-treatment failure and overall survival. This trial was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by ethic committees and health authorities of the participating centres and countries. All patients provided written informed consent before inclusion in the study.

Eligibility criteria. Eligible patients were female, ≥18 years, with histologically confirmed HER2-positive breast cancer by Immuno Histo Chemistry (IHC) 0-2+ confirmed as Fluorescent in Situ Hybridization (FISH) positive or IHC 3+ on local evaluation, documented metastatic disease previously untreated by chemotherapy, Karnofsky performance status ≥70%, at least one measurable lesion according to RECIST 1.0 criteria (23) and a life expectancy ≥16 weeks. Adjuvant or neo-adjuvant chemotherapy containing an anthracycline and/or a taxane was allowed if ≥6 months had elapsed between the last dose of chemotherapy and documentation of relapse. Any number of prior hormone therapies for advanced disease was allowed. Patients were required to have adequate bone marrow, hepatic and renal functions, indicated by: haemoglobin ≥10 g/dl, absolute neutrophil count ≥2× 10^9/l, platelet count ≥100× 10^9/l, total serum bilirubin ≤1.5× upper normal limit (UNL), AST/ALT ≤2.5× UNL, (≤3.5× UNL in patients with liver metastases), alkaline phosphatase ≤2.5 UNL (or ≤5 UNL if bone metastases present) and creatinine clearance >50 ml/min (calculated using the Cockroft and Gault formula). Patients were ineligible if they had received prior chemotherapy in the metastatic setting or previous exposure to a vinca alkaloid, capecitabine or trastuzumab. Other key exclusion criteria were serious illness or medical conditions such as cardiac disease, unstable diabetes, uncontrolled hypercalcaemia, severe peripheral neuropathy, active infection or previous organ allograft. Patients were also excluded if they were pregnant or lactating, required concurrent use of the antiviral sorivudine or a chemically related analogue such as brivudine, had clinical central nervous system or leptomeningeal metastases, had malabsorption disease that might affect absorption or oral chemotherapy, had possible hypersensitivity to fluoropyrimidine therapy, had participated in another clinical trial with any investigational drug within 30 days prior to the study inclusion, or had a history of another malignancy except fully resected basal cell carcinoma of the skin or excised carcinoma *in situ* of the cervix.

Treatment plan. Treatment was given in 3-weekly cycles. Oral vinorelbine was administered at 60 mg/m^2 on days 1 and 8 of the first cycle and escalated to 80 mg/m^2 at cycle 2 and subsequent cycles in the absence of grade 3 or 4 haematological toxicity. Capecitabine was given at a dose of 1000 mg/m^2 twice daily, days 1 to 14 (750 mg/m^2 twice daily for patients ≥65 years). Trastuzumab was given intravenously at 4 mg/kg on day 1 (loading dose), then 2 mg/kg weekly starting on day 8. Treatment was continued until disease progression, unacceptable toxicity or patient's refusal. If one of the three agents was permanently stopped, the patient was considered as withdrawn from the study.

Dose modifications. Dose adjustments or treatment delays were made in the event of dose-limiting haematological or non-haematological toxicities. If study treatment could not be administered due to any toxicity for more than 14 days from the anticipated day 1 of a subsequent cycle, treatment was permanently discontinued. Thus the maximum interval between the start of one cycle and the next was five weeks. Oral vinorelbine and capecitabine were not administered if patients had grade 2 or more neutropenia. Following one episode of grade 3 or 4 neutropenia, the dose of oral vinorelbine was permanently decreased to 60 mg/m^2 for all subsequent cycles. Patients experiencing grade 3 or 4 neutropenia, with or without fever, were allowed to receive granulocyte colony-stimulating factor (G-CSF) in the subsequent

cycles at the investigator's discretion. If AST/ALT/alkaline phosphatase increased to >5.0 UNL, or if bilirubin increased to >1.5 UNL, both agents were withheld and reassessment was performed a week later. If grade 2 or more diarrhea or hand-foot syndrome occurred, administration of capecitabine was interrupted until it resolved to grade 0 or 1, and doses were reduced by 25% (if grade 3) or 50% (if grade 4) for subsequent cycles. No dose adjustment for trastuzumab was planned in the trial.

Study assessments. Each patient underwent baseline assessments, including medical history, physical examination, performance status, HER2 testing (either on the primary tumour or a metastatic site), electrocardiogram and left ventricular ejection fraction (LVEF) assessment. Tumour measurements were evaluated by computed tomography (CT). Complete blood cell counts were performed within two days before each oral vinorelbine administration. Responses were assessed every two cycles until disease progression or more frequently if progression was clinically suspected. The overall response achieved, according to RECIST 1.0 criteria (23), was reported for each patient. A complete response (CR) required complete disappearance of all lesions, and a partial response (PR) required at least a 30% decrease of the sum of the longest diameters of target lesions. Both CR and PR had to be confirmed at least four weeks later. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Progressive Disease (PD). PD was defined as at least a 20% increase in the sum of longest diameters of target lesions or the appearance of new lesions. Clinical benefit was defined as patients achieving CR, PR or SD maintained for a minimum of six months. Adverse events and medical history were recorded throughout the study. The severity of adverse events was graded according to NCI common toxicity criteria version 2.0.

Statistical analysis. The one-sample multiple testing procedure for phase II clinical trials as described by Fleming (24) was used. This procedure employs the standard single stage test procedure at the last one of two pre-specified tests, while allowing for early termination (should extreme results be seen) and essentially preserving the size and power of the single-stage procedure. Based on a type I error rate of less than 5% and an approximately 80% power to reject the null hypothesis of a 30% objective response rate (complete or partial), a sample size of 45 patients was needed. Assuming 10% of patients to be non-evaluable, 50 patients were recruited into the study. All patients who commenced treatment were included in the intent-to-treat (ITT) analysis and were analysed for safety. The evaluable population was defined as all patients eligible for the trial that underwent full evaluation of target and non-target lesions and had received at least two cycles of study treatment (including patients with PD documented before the second cycle). Response rate and clinical benefit were tabulated together with 95% CI following the exact method. The Kaplan Meier method was applied to overall survival, progression-free survival and duration of response. Subset analysis (according to baseline characteristics) was performed for response rate.

Results

Patients' characteristics. Between March 2004 and June 2006, 50 patients with metastatic breast cancer were enrolled from 13 sites in seven countries. Six of the patients included in the trial were not evaluable for response, but were included in the ITT analysis: three patients were not assessable as a result of premature study discontinuation because of adverse events, for two patients full evaluation of all target and non-target lesions was lacking and one patient was not eligible for the study (no measurable disease, as defined in the protocol). Therefore, 44 patients with measurable disease were assessable for disease response per protocol. Visceral metastases were present in 82% of patients with three quarters having two or more sites of metastatic disease (Table I). More than half (54%) had received prior (neo)adjuvant chemotherapy, including an anthracycline and/or a taxane in nearly 90% of this group. All the included patients had a HER2-positive status: 82% of them being IHC 3+ and 18% FISH+.

Table I. *Patients' characteristics*.

Characteristic	N=50	(%)
Median age, years		
Range	53.5 (30.0-89.0)	
<65	41	82
≥65	9	18
Karnofsky performance status at baseline		
70/80	11	22
90/100	39	78
Prior chemotherapy (early-stage)	27	54
Type of chemotherapy		
Anthracycline-based without taxane	15	30
Anthracycline + taxane	8	16
Taxane only	1	2
CMF (cyclophosphamide, methotrexate, fluorouracil)	3	6
Prior hormone therapy	19	38
Number of metastatic sites		
1	14	28
2	19	38
>2	17	34
Visceral involvement	41	82
Metastatic sites		
Liver / lung	29/24	58/48
Bone	20	40
Skin/Soft tissue	4/3	8/6

Clinical efficacy. The objective response rate was 77% among the 44 evaluable patients [95% CI=62-89%], including CR in 21%. The clinical benefit was 93% [95% CI=81-99%]. In the Intent to Treat population, the objective response rate was of 68% [95% CI=53-80%]. Median time to response was 1.5 (range=1.2-9.3) months and median duration of response was 13.3 [95% CI=9.8-15.7] months (Table II). A subanalysis of responses according to patient characteristics is shown in Table III. Of note, the response rate in patients with visceral metastases (72%) was similar to the rate in the overall

Table II. *Response to treatment*.

Objective response rate (RECIST)	Evaluable population n=44	ITT population n=50
CR	21%	18%
PR	57%	50%
Objective response (CR+PR)	77%	68%
[95% CI]	[62-89]	[53-80]
SD	18%	16%
PD	5%	4%
Clinical benefit (CR+PR+SD ≥6 months)	93%	82%
[95% CI]	[81-99]	[69-91]
Median time to response (range)	1.5 months (1.2-9.3)	
Median duration of response [95% CI]	13.3 months [9.8-15.7]	

Table III. *Subanalysis of responses according to patients' characteristics*.

Overall response rate (RECIST)	(%)
All evaluable patients (n=44)	77
Visceral metastases (n=36)	72
Liver metastases (n=25)	68
No prior chemotherapy (n=19)	90
Prior anthracycline without taxane (n=14)	79
Prior anthracycline with taxane (n=7)	57
ER-positive (n=18)	72
ER-negative (n=22)	86

Table IV. *Treatment-related adverse events*.

Adverse events by NCI/CTC v.2.0	Per patient (%) N=49*		Per cycle (%) N=793	
	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	2.0	-	0.1	-
Leukopenia	16.3	12.2	2.0	0.8
Neutropenia	36.7	34.7	6.9	2.4
Thrombocytopenia	-	-	-	-
Febrile Neutropenia**	8.0	0.5		
	Per patient (%) N=50		Per cycle (%) N=800	
	Grade 3	Grade 4	Grade 3	Grade 4
Nausea	4.0	-	0.3	-
Vomiting	10.0	2.0	0.8	0.1
Diarrhea	16.0	-	1.1	-
Constipation	2.0	-	0.1	-
Stomatitis	2.0	2.0	0.1	0.1
Hand-foot syndrome	20.0	-	1.3	-
Fatigue	6.0	2.0	0.4	0.1
Infection with G3/4 neutropenia	4.0	-	0.3	-
Infection without G3/4 neutropenia	2.0	-	0.1	-
Thrombosis/embolism	-	2.0	-	0.1
LVEF decline	2.0	2.0	0.1	0.1
	Grade 1	Grade 2		
Alopecia	18.0	14.0		

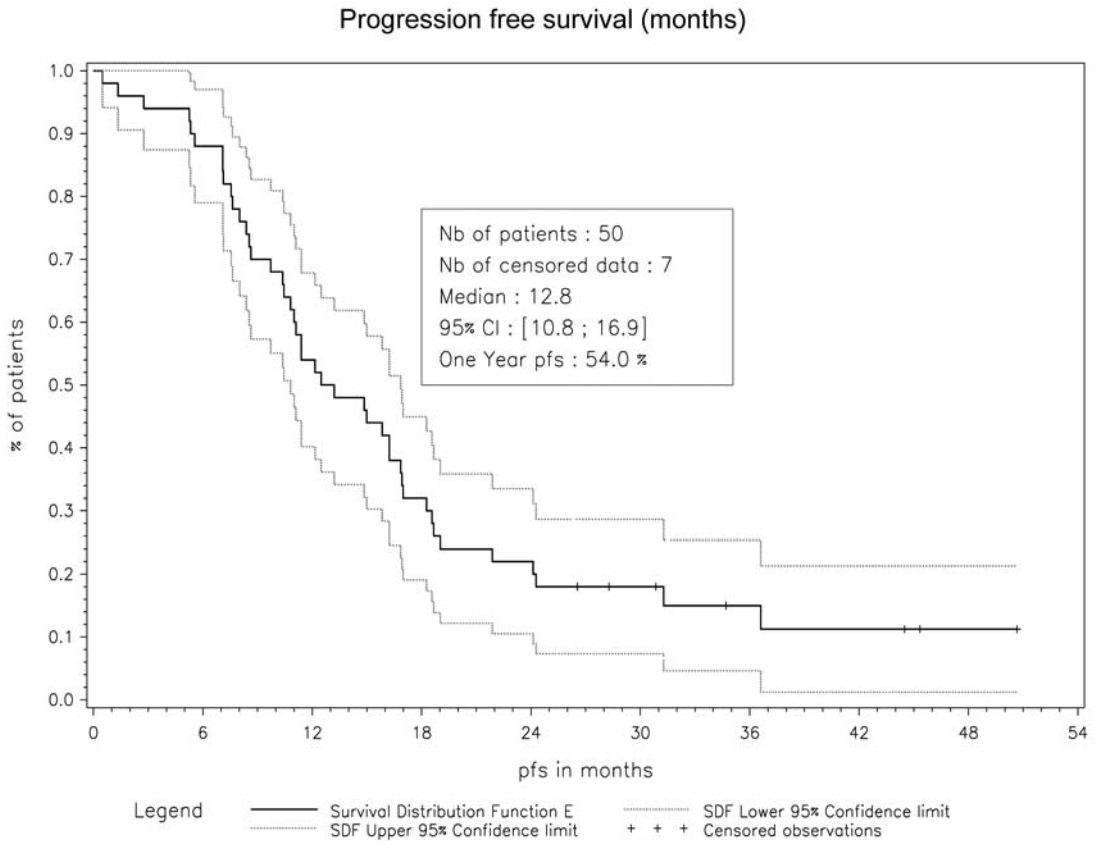
*One patient was not evaluable for haematological adverse events. **50 patients and 800 cycles were evaluable for febrile neutropenia.

population. Median progression-free survival was 12.8 [95% CI=10.8-16.9] months (Figure 1), median time-to-treatment failure was 8.0 [95% CI=6.4-11.4] months and median overall survival was 47.0 [95% CI=30.5-64.3] months (Figure 2).

Treatment-related toxicity. Table IV shows the incidence of the most common grade 3-4 side-effects related to treatment. The most frequent grade 3-4 haematological toxicity was neutropenia which was observed in 71% of patients. Four patients (8%) experienced an episode of febrile neutropenia. Two additional patients (4%) had documented infection associated with grade 3-4 neutropenia. All haematological events resolved after adequate clinical management. The most frequent non-haematological grade 3 toxicity occurring in >5% of patients were vomiting, diarrhea and hand-foot syndrome. Only 14% of patients experienced grade 2 alopecia. Two patients (4%) experienced grade 3 LVEF decline following one cycle despite normal ejection fraction prior to therapy, and discontinued all study treatment. One of these patients presented with ischaemic chest pain that was considered a fluoropyrimidine-related cardiotoxicity (25). Both patients recovered from these cardiovascular events. An additional patient who was aged 75 years experienced a fatal cardiac arrest of uncertain cause following the first cycle of treatment. A median number of 10 cycles was delivered (range=1-81), with 72% of patients receiving more than six cycles, 58% more than eight cycles and 32% more than 16 cycles. The median relative dose intensity of oral vinorelbine, capecitabine and trastuzumab was 76%, 78% and 96%, respectively. Dose escalation of oral vinorelbine was achieved in more than 80% of the patients. The median number of trastuzumab administrations was 30 (range 1-251). At the time of analysis, three patients were still receiving study treatment.

Discussion

This triple drug combination demonstrated high efficacy in HER2-positive metastatic breast cancer with a response rate of 77% [95% CI=62-89%], median progression-free survival of 12.8 [95% CI=10.8-16.9] months and a median duration of



Time (in months)	6	12	18	24	30	36	42	48
Patients at risk	44	27	16	11	7	4	3	1

Figure 1. *Progression-free survival (PFS). Intent to Treat analysis.*

response of 13.3 [95% CI=9.8-15.7] months. Moreover, similar rates of objective response were seen in patients with visceral metastases. Clinical benefit, which has been shown to be an important end-point, was obtained in more than 90% of patients. The median overall survival of 47.0 [95% CI=30.5-64.3] months observed for evaluable patients in our trial compares favourably to other combination regimens in this setting (26-28). An Italian study utilising the same three-drug combination, demonstrated a response rate of 88% and a median progression-free survival of 12 months, lending further support to the efficacy of this regimen (29). Trastuzumab in combination with chemotherapy in the metastatic setting has been extensively studied. Administration with anthracyclines is effective, but a higher rate of cardiac toxicity is seen and thus trastuzumab is more commonly given with a taxane (paclitaxel or docetaxel) (27, 30). The activity observed with the combination of oral vinorelbine and capecitabine in our study compares favourably to the taxane-based regimens. The toxicities associated with the triple combination of oral vinorelbine, capecitabine and trastuzumab were predictable and manageable. As in other phase II studies evaluating this regimen, despite grade 3 or 4 myelosuppression occurring in more than 70% of patients, the incidence of neutropenic infection was infrequent. The good tolerability of the combination is apparent from the long duration of therapy in many responding patients in our study. The median number of cycles given was 10, and some patients received this treatment for more than one year. Several surveys showed that provided efficacy and tolerability are not compromised, most patients prefer oral to intravenous chemotherapy (31, 32). Oral chemotherapy may reduce anxiety in patients who are afraid of injections. Whether it is administered at home or at a

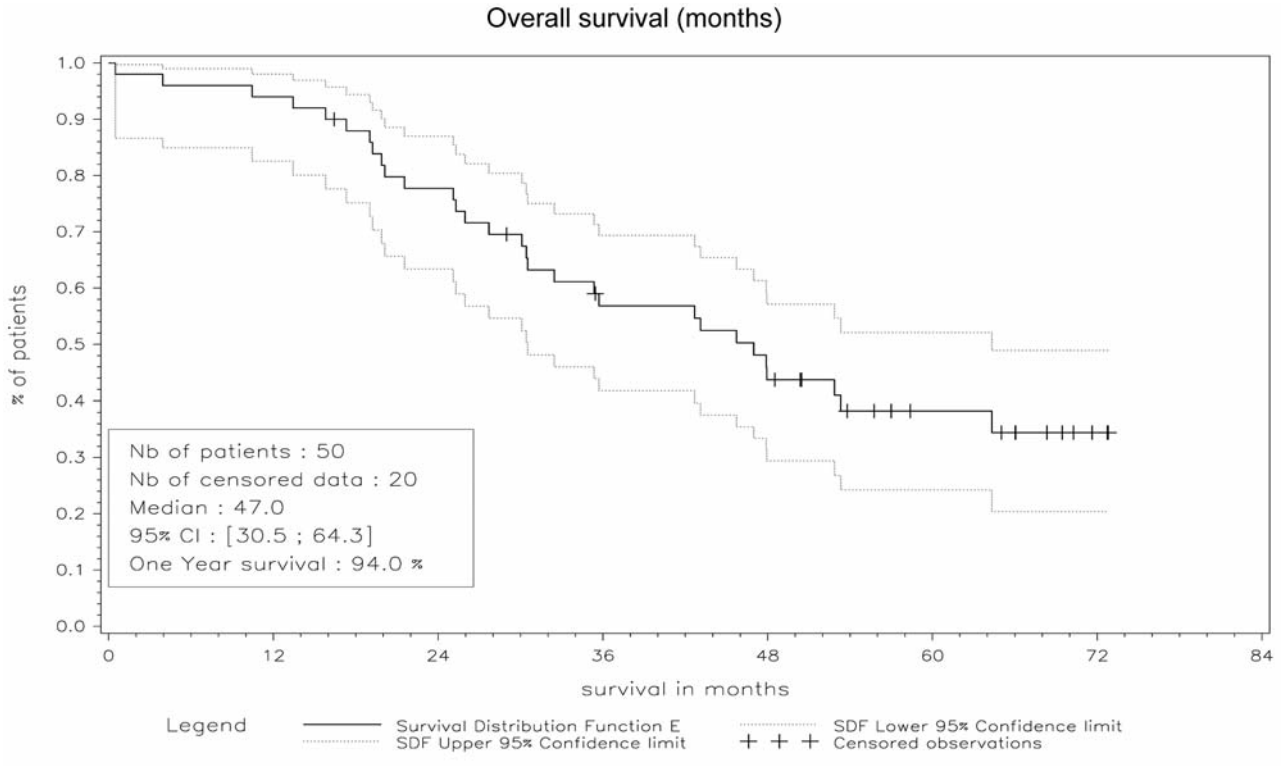


Figure 2. *Overall survival (OS). Intent to Treat analysis.*

hospital, it reduces treatment-related constraints by requiring fewer and shorter hospital visits and has a smaller impact on daily activities (32). The benefits of an oral chemotherapy for patients with metastatic breast cancer in the HER2-positive setting may provide even greater patient satisfaction as a subcutaneous formulation of trastuzumab is now available. A recent phase III trial showed that subcutaneous trastuzumab, administered over five minutes, has a pharmacokinetic profile and efficacy which is non-inferior to standard intravenous trastuzumab, with a similar safety profile (33). In conclusion, the combination of oral vinorelbine, capecitabine and trastuzumab evaluated in this study is effective and well-tolerated and may be seen as a valid alternative first-line treatment for patients with HER2-positive, metastatic breast cancer.

Conflicts of Interest

Nathalie Vaissiere and Gustavo Villanova are employees of Pierre Fabre. All remaining Authors have declared no conflicts of interest.

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