

Use of trastuzumab in HER2-positive metastatic breast cancer beyond disease progression: a systematic review of published studies

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ABSTRACT

Aims and background. Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of ErbB, has determined clinical benefit for women affected by metastatic or early stage HER2-positive breast cancer and never previously treated with trastuzumab. Trastuzumab is generally used as first-line treatment of HER2+ metastatic breast cancer and is currently administered beyond progression even without clear evidence supporting such clinical practice. In fact, HER2-positive metastatic breast cancer has a high risk of progressing after first-line therapy, and second-line treatments vary. The aim of the study was to investigate by a systematic review the efficacy of trastuzumab-based treatments beyond progression in HER2-positive metastatic breast cancer.

Materials and methods. We performed a systematic review using Medline, Embase and Cochrane Library data bases and publications in principal meetings or congresses of oncology in Europe and America until September 2008. The main selection criterion was the reporting of time to progression, calculated from the start of each trastuzumab-based therapy to the date of progressive disease or death.

Results. Twelve studies were selected that included a total of 516 patients. The weighted mean time to progression was 23.66 weeks (standard deviation, 4.37) and the median was 26 weeks (range, 13-39). Interestingly, combined trastuzumab plus vinorelbine treatment showed a lower mean and median time to progression (20.59 and 19.57 weeks, respectively), whereas trastuzumab plus capecitabine yielded a mean time to progression of 30.33 weeks.

Conclusions. The added value of the present study has been to provide a quantitative summary measure of time to progression which can be used for comparisons between current and future available regimens. Free full text available at www.tumori-online.it

Introduction

Breast cancer represents a huge public health problem, as it is the first diagnosed cancer in women of all ages in Italy and worldwide^{1,2}. It is also the primary cause of cancer mortality in women worldwide¹. The prognosis, as well as treatment success, is influenced by different factors including cancer size and stage, histologic type, age and also genetic and biological markers^{3,4}. Both growth factor receptors ErbB1 and ErbB2 (also known as HER-1 and HER-2/neu) have been shown to be overexpressed in approximately 20-30% of primary breast cancers⁵⁻⁷. In such cases, cancer prognosis is very poor since the ErbB family activates tyrosine kinase-mediated intracellular signals, which promote cell proliferation⁸. Patients with HER2-positive (HER2+)

Key words: beyond progression, Herceptin, metastatic breast cancer, trastuzumab.

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breast cancer are at high risk of progression and death^{6,9}. HER2+ breast cancers are very difficult to treat and manage because of the high incidence of metastasis to bone, brain and liver¹⁰. In fact, they are often diagnosed in stage IV as advanced, not amenable to cure.

The development of new treatment options has expanded the possibility of cure in advanced breast cancer. The National Institute of Clinical Excellence, in 2001, recommended the use of taxanes, docetaxel and paclitaxel to treat patients with advanced breast cancer for whom chemotherapy with anthracyclines was no longer appropriate¹¹, and, in 2002, recommended the use of trastuzumab either in combination or in monotherapy, according to previous treatment options, for women with HER2+ advanced breast cancer⁹.

Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of ErbB2, produces a clear clinical advantage in women affected by metastatic or early stage HER2 over-expressing breast cancers who have never received trastuzumab before¹²⁻¹⁴. Trastuzumab is approved as first-line treatment of HER2+ metastatic breast cancer (MBC), but currently is also administered beyond progression without clear evidence supporting this clinical practice. In fact, HER2+ MBC has a high risk, about 84%⁵, of progressing after the first-line therapy, but the outcome of second-line treatments is very different.

In this context, new drugs like lapatinib, an oral, selective, reversible tyrosine kinase inhibitor of both ErbB1 and ErbB2 signaling pathways, is considered a promising alternative to trastuzumab continuation beyond progression. Given the lack of prospective randomized data facing this issue, a systematic review of studies about the use of trastuzumab alone or in combination with other drugs was performed to evaluate the efficacy of trastuzumab-based treatments beyond progression in HER2+ MBC.

Material and methods

Identification of studies

The identification of studies on women affected by HER2+ MBC who continued to receive trastuzumab beyond disease progression was carried out through a search of Medline, Embase and Cochrane Library data bases up to October 2008 using the following terms: trastuzumab or Herceptin and MBC or MBC and beyond progression. Search strategies are reported in Appendices 1 and 2.

Additional studies were identified by the hand searching of references of the original studies and among abstracts or posters presented in the period from January 2007 to October 2008 in the following meetings: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Cancer

Organization (ECCO), San Gallen, Sanantonio, National Cancer Institute European Organization for Research (NCI/EORTC), and the Associazione Italiana di Oncologia Medica (AIOM). The search was restricted to papers written in English and French.

Eligible studies were those which fulfilled the following inclusion criteria. 1) Randomized clinical trials (RCT) or observational studies evaluating the efficacy of continuing trastuzumab in women affected by HER2+ MBC, previously treated with trastuzumab-based therapies (trastuzumab either alone or in combination with chemo- and/or hormone therapy) in the presence of clinical evidence of disease progression. 2) Reporting estimates of clinical outcome, in particular of the time to progression (TTP), calculated from the start of each second-line trastuzumab-based therapy to the date of objective evidence of progressive disease or death. Letters and case reports were thus excluded from the systematic review. When more than one article was published by the same author using the same cases series, the largest study was selected.

Data extraction

Two investigators independently extracted data from each article using a structured sheet and entered them into an Excel data base. The following items were considered: year and design of the study, sample size, median TTP in weeks (given that one year is made up of 52 weeks) for each trastuzumab-based regimen where possible, and details on administered drugs.

Statistical analysis

The weighted median, mean, standard deviation (SD) and standard error (SE) of median TTP were computed. In order to evaluate the year of publication as a potential predictive variable of TTP estimate, a bivariate analysis was performed using Spearman's coefficient (r). Moreover, a multivariate analysis was performed to estimate the relationship between TTP, year of publication and sample size. The goodness of fit was evaluated using the R^2 coefficient. In order to carry out a sensitivity analysis, a subgroup analysis was performed according to trastuzumab-based regimens (selecting those with trastuzumab plus vinorelbine or trastuzumab plus capecitabine) and sample size greater than or equal to 25 and 30. The statistical significance level was set at $P < 0.05$. Analyses were carried out using the software SPSS version 12.00 for Windows.

Results

Of the 194 articles retrieved, 44 were eligible after abstract selection (Figure 1)¹⁵. After reading full texts, only 16 studies¹⁶⁻³¹ were finally considered eligible for our systematic review (Table 1). Among these, only one

Table 1 - Characteristics of the selected studies

Author(s)	Year	Study design	Therapy	Sample size, no. (no.*)	Type of patients	Previous treatment (subgroups)	Outcome measures
Fountzilias <i>et al.</i> ¹⁶	2003	Retrospective	H ± CT	80	HER2+ previously treated with H and CT & who subsequently progressed & continued on H with or without CT	Anthracycline = 33% TXN = 41% H = 100%	TTP, tumor response
Suzuki <i>et al.</i> ¹⁷	2003	Multicenter phase II	V + H	24	HER2+ who did not respond to or relapsed after administration of trastuzumab in monotherapy or in combination with TXN	Anthracycline = NR TXN = 79% H = 100% Anthracycline + TXN = NR	TTP, tumor response rate & toxicity
Gelmon <i>et al.</i> ¹⁸	2004	Multicenter retrospective	H ± CT	105 (63)	HER2+ who received ≥2 H-containing regimens	Anthracycline = 39% TXN = 48% H = 100%	CR, PR, TTP
Garcia-Sáenz <i>et al.</i> ¹⁹	2005	Retrospective	H ± CT	58 (31)	HER2+ previously treated with H, 31 of whom continued an H-containing regimen after cancer progression	NR	TTP
Bartsch <i>et al.</i> ²⁰	2006	Prospective observational	H + CT	54	HER2+ after one earlier H-containing regimen	Anthracycline = 35% TXN = 24% H = 100% Anthracycline + TXN = NR	Disease progression with H treatment
Adamo <i>et al.</i> ²¹	2007 ^o	Retrospective	H + CT	70 (26)	HER2+ who received an H-based regimen	CT adjuvant = 46 CT, prior therapy for metastatic disease = 25	TTP and OS
Bartsch <i>et al.</i> ²²	2007	Prospective	H + X	40 (21)	X and H combination in heavily pretreated pts with HER2+MBC after earlier H exposure	Anthracycline = NR TXN = NR H = 100% Anthracycline + TXN = 57.3%	TTP, CR & PR
Montemurro <i>et al.</i> ²³	2007 ^{§A}	Retrospective	H ± CT or endocrine therapy	279 (83)	HER2+ who received H-based therapy, 83 of whom continued H beyond disease progression in addition to H-containing regimen		TTP, OS
Bartsch <i>et al.</i> ²⁴	2008	Prospective	H + G	29 (9)	HER2+ pretreated with anthracyclines, TXN & H	Anthracycline = NR TXN = 72.4% H = NR	TTP, CR, PR, ORR: CR + PR & toxicity
Canello <i>et al.</i> ²⁵	2008	Retrospective	H+A/TXN	101 (55)	HER2+ who received first-line H-based treatment	H = 100%	TTP & OS of pts who received second line with H vs pts who stopped H
Fabi <i>et al.</i> ²⁶	2008	Retrospective observational	H + CT	59 (37)	HER2+ with H-based regimen	Anthracycline = 20% TXN = 4% Anthracycline + TXN = 54%	TTP, OS, OR, PPS, CB
Tokajuk <i>et al.</i> ²⁷	2008 [^]	Retrospective	H ± CT	46 (33)	HER2+	NR	TTP in H therapy beyond disease progression for MBC pts treated
von Minckwitz <i>et al.</i> ^{28,29}	2008, 2009 [^]	RCT	H ± C	156 (78)	HER2+ previously treated with H given alone or in combination with further chemotherapies	H + TXN = 71% H = 275	TTP & OS after second-line treatment with combination of C + H vs C

A, anthracycline; C, capecitabine; CI, cisplatin; CT, chemotherapy; G, gemcitabin; H, Herceptin, trastuzumab; Pz, pertuzumab; TXL, paclitaxel; TXN, taxane; TXT, docetaxel; V, vinorelbine; CB, clinical benefit; CR, complete response; PR, partial response; OR, overall response; ORR, overall response rate; OS, overall survival; PPS, post-progression survival, TTP, time to progression.

*no. in parenthesis, patients who received a second Herceptin-containing regimen.

^oAdamo *et al.* 2007²¹ included the same results contained in the abstract of Rossello R, AIOM Congress 2007³², and in this case it was considered as one paper.

[§]Montemurro *et al.* 2007²³ included results of other two studies, Montemurro *et al.* 2006 and 2008^{30,31}.

[^]Poster abstract at ASCO 2008, followed by *in-extenso* publication.

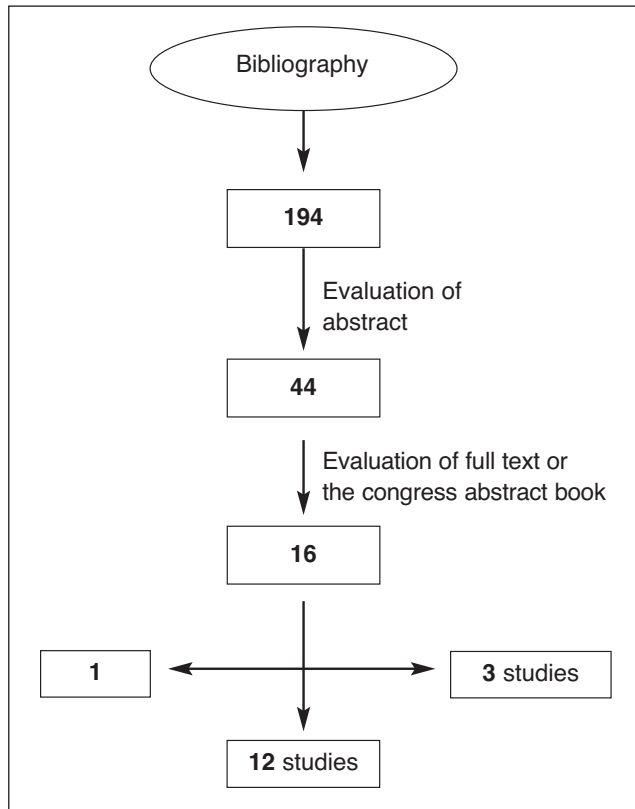


Figure 1 - Flowchart of selection of the studies.

study, von Minckwitz *et al.*²⁸, was an RCT, published in April 2009 (previously presented as a poster in 2008 ASCO Annual Meeting)²⁹, so it was not included in the same evaluation performed for observational studies, in order to maintain the homogeneity of study design. Owing to data overlap between the previous studies, 3 of them were excluded from the final analysis³⁰⁻³² (legend, Table 1).

In the only RCT, median TTP was 8.2 months (34 weeks) in the experimental arm (trastuzumab + capecitabine) compared to 5.6 months (24 weeks) in the control arm (capecitabine alone). Further analysis was not possible due to the lack of other RCT²⁸.

Concerning nonrandomized studies, overall 12 observational studies were considered¹⁶⁻²⁷, comprising a total of 516 patients affected by HER2+ MBC. The weighted mean TTP was 23.66 weeks (SD = 4.37; SE = 1.17) and the median, 26 weeks (range, 13-39) (Table 2).

Figure 2 shows that there was a positive but not significant correlation between TTP and publication year, with a Spearman's coefficient of $r = 0.246$ ($P = 0.397$). The correlation between TTP and sample size was negative and not significant, $r = -0.075$ ($P = 0.798$). Multivariate analysis did not show a significant association between TTP and publication year ($\beta = 1.43$; $P = 0.202$) or sample size ($\beta = 0.034$; $P = 0.712$). The goodness of fit for the model was summarized by the coefficient $R^2 = 0.153$ (Table 3).

Table 2 - Descriptive data of the selected studies (16-27). Pooled measures weighted by the number of observations

Authors (year)	Treatment ^o	No.	% weight on total	Median TTP (weeks)	Range (weeks)		95% CI	
					Min	Max	Low	High
Adamo <i>et al.</i> ²¹ (2007)	H + V/TXN/DOX/G	26	4.13	39.00	13.00	99.67	NR	NR
Bartsch <i>et al.</i> ²⁰ (2006)	H + V/X/G/D	54	8.57	26.00	4.33	104.00	NR	NR
Bartsch <i>et al.</i> ²² (2007)	H + X	21	3.33	30.33	8.67	91.00	12.96	47.71
Bartsch <i>et al.</i> ²⁴ (2008)	H + G	9	1.43	26.00	4.33	30.33	21.23	30.77
Canello <i>et al.</i> ²⁵ (2008)	H + A/TXN	55	8.73	22.75	5.42	148.20	NR	NR
Fabi <i>et al.</i> ²⁶ (2008)	H + V/TXN/X/CTX/G/ CBDCA	37	5.87	29.03	NR	NR	16.90	40.73
Fountzilias <i>et al.</i> ¹⁶ (2003)	H + V/G	80	12.70	22.53	2.17	7.37	NR	NR
García-Sáenz <i>et al.</i> ¹⁹ (2005)	H + TXN/V	31	4.92	13.00	4.33	95.33	NR	NR
Gelmon <i>et al.</i> ¹⁸ (2004)	H + V	33	5.24	26.00	3.00	108.00	NR	NR
Gelmon <i>et al.</i> ¹⁸ (2004)	H + P	20	3.17	24.00	3.00	72.00	NR	NR
Gelmon <i>et al.</i> ¹⁸ (2004)	H	10	1.59	30.50	18.00	68.00	NR	NR
Montemurro <i>et al.</i> ²³ (2007)*	H + V/TXN/DOX/X	83	13.17	36.40	NR	NR	NR	NR
Suzuki <i>et al.</i> ¹⁷ (2003)	H + V	24	3.81	13.14	5.14	32.14	NR	NR
Tokajuk <i>et al.</i> ²⁷ (2008)*	H	33	5.24	19.93	0.00	190.67	NR	NR
Total	516							
Median TTP (wks)	26							
Minimum TTP (wks)	13.00							
Maximum TTP (wks)	39.00							
Weighted mean (wks)	23.66							
Weighted SD (wks)	4.37							
Weighted SE (wks)	1.17							

CBDCA, carboplatin; CI, cisplatin; CT, chemotherapy; CTX, cyclophosphamide; D, docetaxel; DOX, doxorubicin; G, gemcitabine; H, Herceptin, trastuzumab; P, paclitaxel; TXN, taxane; V, vinorelbine; X, capecitabine; NR, not reported.

^o / = or, + = and.

*Congress abstract.

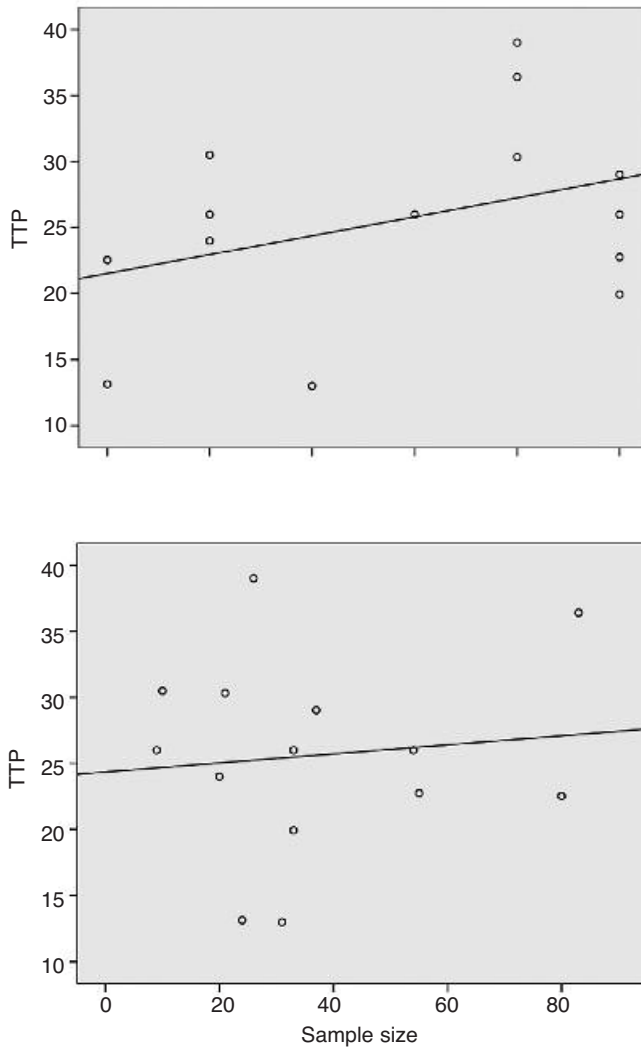


Figure 2 - Scatter plots of median time to progression (TTP) versus publication year and sample size.

Table 3 - Multivariate linear regression

Covariates	Coeff.	P	95% CI
Publication year	1.434	0.202	-0.892; 3.760
Sample size	0.034	0.712	-0.162; 0.230
R ² = 0.153			

The subgroup analyses for observational studies are reported in Table 4. There were 9 studies with a sample size ≥ 25 and 8 with ≥ 30 . The combination trastuzumab + vinorelbine was evaluated in two studies, whereas only Bartsch *et al.*²² investigated the combination trastuzumab + capecitabine. After grouping for sample size, it resulted that the mean and the median values of TTP of the group with sample size ≥ 25 were similar to the pooled ones; in the group with sample size ≥ 30 a slight

Table 4 - Sensitivity analysis according to sample size and treatment combination

	Pooled	N ≥ 25	N ≥ 30	H + V
Number of studies*	14	9	8	2
Number of patients	516	432	406	57
Median TTP (weeks)	26.00	26.00	24.38	19.57
Minimum TTP	13.00	13.00	13.00	3.00
Maximum TTP	39.00	39.00	36.40	28.00
Weighted mean TTP	23.66	23.69	22.71	20.59
Weighted SD	4.37	7.27	7.44	40.30
Weighted SE	1.17	2.42	2.63	28.49

*Observations represent the number of selected studies stratified by treatment.
N, sample size; H, Herceptin, trastuzumab; V, vinorelbine.

decrease in mean and median was observed. However, the trastuzumab + vinorelbine combination on aggregate showed a weighted mean TTP of 20.59 weeks, which was lower than the mean and median TTP reported by Bartsch *et al.*²², who investigated trastuzumab + capecitabine combination therapy (mean, 30.33 weeks, Table 2).

Discussion

The current clinical practice of continuing trastuzumab beyond disease progression in women with HER2+ MBC is still debated due to a substantial lack of scientific evidence since randomized studies adequately powered have not been completed. In addition, this therapeutic strategy deviates from a well-established paradigm of stopping and switching drugs or interventions when disease progression becomes clinically evident. The safety and feasibility of continuing trastuzumab beyond progression have been mostly evaluated by retrospectively collecting medical records of patients who stopped or continued trastuzumab¹⁶⁻²⁸.

The same critical question has been recently addressed by von Minckwitz *et al.*^{28,29}, who randomly assigned HER2+ MBC patients progressing during previous treatment with trastuzumab to receive either capecitabine alone or with trastuzumab. A significant improvement in overall response and TTP with the capecitabine + trastuzumab regimen was observed, even though a statistically significant impact on survival could not be demonstrated. According to Jahanzeb³³, however, the results of that clinical trial should be interpreted with caution, because the trial was prematurely interrupted due to slow accrual when less than 200 patients had been accrued in 45 months, far less than the intended 482, resulting in a very low or valueless statistical power.

Another reason for closing the trial was the availability of lapatinib + capecitabine data indicating that the same authors were not very confident about data until

then obtained. In fact, they observed that their results could not be easily compared with those of the lapatinib trial³⁴. A trial in which patients are randomly assigned to capecitabine + trastuzumab or lapatinib + capecitabine would better address the objective of directly comparing these combination regimens. To date, only preliminary results of a randomized study³⁵ of lapatinib alone or in combination *versus* trastuzumab in HER2+ MBC patients progressing on T-based therapy have been reported. The study showed the superiority of the doublet (progression-free survival, 12 *vs* 8.1 weeks, $P = 0.008$), demonstrating for the first time the synergy of lapatinib + trastuzumab in a phase III setting and improved clinical outcome without a substantial change in the side effect profile.

In the present study, a systematic review was carried out in order to answer the critical question about effectiveness of continuing trastuzumab therapy beyond progression. Firstly, we searched for phase III trials aiming to provide summary estimates of clinical outcomes (overall survival, TTP, response rate) by means of meta-analysis. However, we found only the aforementioned study of von Minckwitz *et al.*^{28,29}, so data pooling was not statistically possible. Therefore, according to the fact that most data come from observational studies, we systematically reviewed 12 available studies, obtaining a weighted mean TTP of 23.66 weeks (SD = 4.37; SE = 1.17). No significant differences resulted in the analysis of subgroups obtained by stratifying the eligible studies according to sample size (≥ 25 and ≥ 30 patients) or type of trastuzumab-containing combination therapy (capecitabine or vinorelbine). Interestingly, in the study of Bartsch *et al.*²² concerning the combination trastuzumab + capecitabine, median TTP was higher than the weighted pooled estimated mean TTP (30.33 *vs* 23.66 weeks).

The absolute value of the present review is limited by the characteristics of the study sample, including small and heterogeneous series of mainly observational and retrospective investigations. This introduces a bias in our evaluation derived from the design of studies used in the analysis and decreases the strength of our data. However, we can conclude that trastuzumab-based regimens might have activity in HER2+ MBC beyond progression, but only well-designed phase III studies will possibly identify patients who will progress after trastuzumab by keeping in mind other drugs potentially targeting the same biological pathway. In this context, a multidisciplinary approach aimed at evaluating the different aspects of the treatment choice in HER2+ MBC could be useful to bridge current gaps³⁶.

Appendix 1

Search Algorithm (RCT OR randomised clinical trial OR randomized clinical trial) AND (herceptin OR

trastuzumab OR "her-2 overexpression") AND (advanced breast cancer OR breast cancer OR metastases).

Appendix 2

Search Algorithm (trastuzumab OR Herceptin) AND (disease progression OR beyond progression) AND metastatic breast cancer.

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