Single-agent trastuzumab versus trastuzumab plus cytotoxic chemotherapy in metastatic breast cancer: a single-institution experience

Wolfgang J. Köstler[a,e], Günther G. Steger[a,e], Michael Krainer[a,e], Gabriela V. Kornek[a,e], Gottfried J. Locker[a,e], Thomas Brodowicz[a,e], Christine Marosi[a,e], Christian F. Singer[b,e], Gernot Hudelist[d], Werner Rabitsch[c,e], Christoph Wiltschke[a,e] and Christoph C. Zielinski

Trastuzumab has shown significant single-agent activity in patients with Her-2/*neu* overexpressing metastatic breast cancer, and increased response rates, progression-free and overall survival when added to standard chemotherapy. Despite higher response rates, the combination with chemotherapy has higher toxicity and it remains unknown whether single-agent trastuzumab is equally effective as the combined treatment in terms of progression-free and overall survival. We therefore carried out a retrospective multivariate analysis of 117 patients with Her-2/*neu* overexpressing metastatic breast cancer who were treated with trastuzumab with or without chemotherapy at a single institution between November 1999 and December 2003. Response rates tended to be higher in patients receiving trastuzumab in combination with chemotherapy (34 versus 8%, $p=0.060$). However, this did not translate into a benefit in progression-free survival: median (95% confidence interval) progression-free survival was 6.2 (4.45–7.95) months in patients receiving trastuzumab plus chemotherapy versus 4.2 (1.77–6.63) months in those receiving single-agent trastuzumab ($p=0.560$). Likewise, no significant difference in overall survival was observed: 27.0 (19.9–34.0) versus 23.1 (16.2–30.0) months ($p=0.809$). We conclude that in the absence of extensive visceral involvement necessitating a higher response rate, single-agent trastuzumab may be a safe and less-toxic alternative to its combined use with other chemotherapy agents. This needs to be confirmed in prospective randomized trials. *Anti-Cancer Drugs* 16:185–190 © 2005 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2005, **16**:185–190

Keywords: chemotherapy, Her-2/*neu*, metastatic breast cancer, trastuzumab

[a]Clinical Division of Oncology, Department of Medicine I, [b]Clinical Division of Special Gynecology, Department of Gynecology and Obstetrics, [c]Bone Marrow Transplantation Unit, Department of Medicine I, Medical University of Vienna, Vienna, Austria and [d]Ludwig Boltzmann Institute for Clinical Experimental Oncology and [e]Center of Excellence for Clinical & Experimental Oncology (CLEXO), University Hospital of Vienna, Vienna, Austria.

Correspondence to W. J. Köstler, Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, 18–20 Waehringer Guertel, 1090 Vienna, Austria.
Tel: +43 1 40400-4445; fax: +43 1 40400-4451;
e-mail: wolfgang.koestler@meduniwien.ac.at

Received 9 September 2004 **Revised form accepted** 27 October 2004

Introduction

Overexpression of the Her-2/*neu* protein, arising predominantly through amplification of the c-erbB-2/*neu* oncogene, occurs in approximately 25% of breast carcinomas. Her-2/*neu* overexpression has frequently been associated with increased biological aggressiveness resulting in a worse prognosis in both patients with early and metastatic breast cancer as compared to those patients without tumors exhibiting Her-2/*neu* overexpression [1,2].

Trastuzumab, a monoclonal antibody targeting the Her-2/*neu* oncoprotein, has not only shown moderate efficacy when administered as a single-agent in patients with Her-2/*neu* overexpressing metastatic breast cancer [1,3–5], but its combined use with chemotherapy has also prolonged progression-free and overall survival as compared with chemotherapy alone [6–10]. However, the combined modality approach has also incurred toxicity, including the typical side-effects of cytotoxic treatment and an increased rate of congestive heart failure when used in combination with anthracyclines [6]. In addition, despite higher response rates observed in clinical trials evaluating the combined use of trastuzumab and chemotherapy, cross-trial comparisons of the pivotal trastuzumab trials suggest that the addition of chemotherapy may not necessarily translate into a benefit in terms of progression-free and overall survival. It has been postulated that these findings result from the relatively high rates of prolonged disease stabilization observed in the single agent trials (C. Vogel, pers. commun.) [11], which may be attributed to cytostatic effects of trastuzumab which have been observed *in vitro* [12]. To date, however, clinical studies comparing trastuzumab as a single agent with its combined use with chemotherapy are lacking. Therefore, we have performed the present retrospective analysis of

0959-4973

all patients receiving trastuzumab with or without chemotherapy for Her-2/*neu* overexpressing metastatic breast cancer at our institution.

Patients and methods

Data acquisition and patients' characteristics

Since 1999, all patients receiving trastuzumab (Herceptin; Roche Pharmaceuticals, Vienna, Austria) with or without chemotherapy at the discretion of their treating physician according to published protocols [4,6–8,10, 13–15] at our institution are prospectively registered in our 'trastuzumab database'. This database is intended for studying molecular predictors of trastuzumab efficacy and several of our studies evaluating the predictive potential of various molecular markers have been published previously [16–18]. Baseline medical data are documented at initiation of trastuzumab-based treatment and charts are followed on a regular basis, i.e. every 3 months, including review of all imaging studies and interrogation of treating physicians for assessment of response and progression-free and overall survival. A regular crosscheck of pharmacy records is performed to assure that all patients receiving trastuzumab are addressed. All patients are asked to sign an informed consent for the usage of their anonymous medical data for scientific purposes and, to date, none has disagreed to do so. Patients receiving (neo)adjuvant trastuzumab-based treatment for early breast cancer in ongoing multicenter trials are not included. Likewise, patients receiving trastuzumab as 'pseudoadjuvant' treatment after surgical removal or curative radiotherapy of local recurrences or single metastases or patients without measurable disease (e.g. scan-only bone disease or malignant effusions as only site of active disease) are not included.

Thus, all participants in our database had bidimensionally measurable (with both diameters greater than 1.0 cm and at least one lesion with both diameters greater than 1.5 cm) disease with clearly defined margins and radiologically (computed tomography and/or magnetic resonance imaging and/or ultrasound) documented tumor progression (excluding previously irradiated lesions) before initiation of trastuzumab-based treatment. Further exclusion criteria for prospective documentation in the 'database' include ECOG performance status > 2, age ≤ 18 years, estimated life expectancy < 12 weeks, symptomatic CNS metastases, second malignancy with the exception of *in situ* cervical cancer or adequately treated BCC or SCC of the skin, history of congestive heart failure (unless medically controlled) or unstable coronary artery disease, active infection, altered mental status that would prohibit the understanding and giving of informed consent for data acquisition. According to our institutional practice, eligibility for treatment with trastuzumab was determined by immunohistochemical demonstration of Her-2/*neu* grade 2+ or 3+ overexpression (as determined by the HercepTest; Dako, Vienna, Austria), with confirmation of c-erbB-2 amplification by fluorescence *in situ* hybridization for immunohistochemically 2+ cases since mid-2002.

Between November 1999 and August 2004, 131 patients meeting the above criteria have received trastuzumab-based treatment. For the present analysis, patients in whom trastuzumab-based treatment was initiated after 2003 were excluded to allow adequate follow-up time. Thus, the study population comprised a total of 117 (single-agent trastuzumab: $n = 14$) patients with a median (range) follow-up of 35.0 (7.1–56.3) months. In total, 115 patients were eligible for response (two patients receiving trastuzumab plus chemotherapy were excluded from analysis of response because different imaging techniques were used for baseline and restaging examinations). Patients' characteristics are depicted according to treatment (single-agent trastuzumab versus trastuzumab in combination with chemotherapy) in Table 1. In the trastuzumab plus cytotoxic therapy group chemotherapy consisted of vinorelbine ($n = 70$), docetaxel ($n = 12$), paclitaxel ($n = 7$), capecitabine ($n = 5$), epirubicin and docetaxel ($n = 4$), vinorelbine and cisplatin ($n = 2$), paclitaxel and gemcitabine ($n = 2$), and capecitabine and vinorelbine ($n = 1$). Within the observed period, 89% (104 of 117) of patients have experienced disease progression: 86% (12 of 14) of patients receiving single-agent trastuzumab and 89% (92 of 103) of patients additionally receiving chemotherapy. The CNS was the initial site of disease progression in two patients (14%) receiving single-agent trastuzumab (including one patient with pre-existing brain metastases at initiation of treatment with trastuzumab) and represented the first site of disease progression in seven (7%) patients treated with trastuzumab plus chemotherapy (including three patients with known CNS metastases at initiation of treatment with trastuzumab). Treatment was discontinued in 108 patients because of disease progression ($n = 104$), hematologic ($n = 1$) or cardiac ($n = 1$) toxicity or patient denial ($n = 2$), whilst nine (8%) patients were still undergoing trastuzumab-based therapy at the time of the present analysis. Fifty-four percent (63 of 117) of patients had died: 57% (eight of 14) of patients treated with trastuzumab alone and 53% (55 of 103) of patients in the combined modality treatment—and all deaths were attributed to disease progression. No patient was lost to follow-up. Median [95% confidence interval (CI)] progression-free and overall survival calculated from the survival function were 5.9 (95% CI 3.9–7.9) and 27.0 (95% CI 19.4–34.5) months, respectively.

Lesion measurement and evaluation of response to treatment

Restaging was performed every 8–12 weeks (or earlier if disease progression was clinically evident) according to the discretion of the treating physician. Radiology reports

Table 1 Patients characteristics according to type of treatment

	Single-agent trastuzumab ($n=14$)	Trastuzumab plus chemotherapy ($n=103$)	p
Age (years) [median (range)]	52.2 (39.2–67.8)	54.4 (27.6–83.9)	0.496[c]
Her-2/*neu* expression [*n* (%)]			
grade 2+ (FISH+: 3, FISH unknown: 6)	2 (14%)	14 (14%)	
grade 3+	12 (86%)	89(86%)	0.626[a]
Hormone receptor status [*n* (%)]			
ER^+PgR^+	3 (21)	17 (17)	0.705[a]
ER^+PgR^-	4 (29)	18 (17)	0.297[a]
ER^-PgR^+	1 (7)	2 (2)	0.320[a]
ER^-PgR^-	4 (29)	60 (58)	0.069[a]
unknown	2 (14)	6 (6)	
Histologic type [*n* (%)]			
ductal	11 (79)	87 (84)	
other	3 (21)	15 (15)	0.454[a]
unknown	0 (0)	1 (1)	
Grading [*n* (%)]			
1	1 (7)	2 (2)	
2	3 (21)	20 (19)	
3	10 (71)	79 (77)	0.510[b]
unknown	0 (0)	2 (2)	
Sites of active disease [*n* (%)]			
breast (primary or local recurrence)	4 (29)	21 (20)	0.494[a]
axilla	2 (14)	21 (20)	0.733[a]
liver	5 (36)	50 (49)	0.403[a]
lung	3 (21)	42 (41)	0.242[a]
skin/soft tissue	3 (21)	22 (21)	1.000[a]
CNS	1 (7)	4 (4)	0.481[a]
distant lymph nodes	4 (29)	45 (44)	0.389[a]
bone	10 (71)	53 (52)	0.253[a]
other	6 (43)	31 (30)	0.367[a]
No. of organs affected by metastatic disease [*n* (%)]			
1 or 2	6 (43)	54 (52)	
>2	8 (57)	49 (48)	0.576[a]
Metastatic disease to visceral organs [*n* (%)]	6 (43)	73 (71)	0.064[a]
Recurrence-free interval (months) [median (range)]	21.9 (0.0–108.6)	20.7 (0.0–180.7)	0.290[c]
Prior adjuvant chemotherapy [*n* (%)]	10 (71)	64 (62)	0.569[a]
Prior endocrine therapy (adjuvant and/or metastatic) [*n* (%)]	4 (29)	21 (20)	0.494[a]
No. of previous chemotherapeutic regimens for metastatic disease [*n* (%)]			
0	11 (79)	66 (64)	
1	2 (14)	23 (22)	
≥ 2	1 (7)	14 (14)	0.750[b]
ECOG PS [*n* (%)]			
0	3 (21)	21 (20)	
1	8 (57)	68 (66)	
2	3 (21)	14 (14)	0.713[a]
Ca 15-3 level at baseline (kU/l) (mean ± SD)	222 ± 404	226 ± 840	0.182[c]

[a]Fisher's exact test (two-sided).
[b]Pearson χ^2.
[c]Mann–Whitney *U*-test.

and, where available, images were reviewed independently by two of the investigators. Responses were categorized according to Southwest Oncology Group (SWOG) response criteria and endpoint definitions [19]. In brief, complete response (CR) was defined as a complete disappearance of any tumor-related symptoms and all lesions in imaging studies, without appearance of any new lesions. Partial response (PR) was defined as more than 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions and at least stabilization of all non-measurable lesions lasting for a minimum of 4 weeks. PD was defined as a more than 25% increase in the sum of products of all measurable lesions, an unequivocal increase of non-measurable disease or the appearance of new lesions. Disease was classified as being stable (SD) if no criteria for classifying responses as CR, PR or PD were met. Response confirmation 4 weeks after initial response assessment had been performed in a minority of patients only. To account for this weakness, patients with CR, PR or SD demonstrating disease progression within the subsequent 2 months were censored as therapeutic failures (PD).

Statistical analysis

Frequencies of patients' characteristics and response rates were compared by Fisher's exact test (two-sided) and Pearson's χ^2-square test, respectively. Multiple logistic regression analyses were used to determine whether the type of treatment (single-agent trastuzumab versus trastuzumab in combination with chemotherapy) could predict response or clinical benefit (CR or PR or

SD lasting 6 months or more). Grade of Her-2/*neu* overexpression (2+ versus 3+), estrogen and progesterone receptor status (with specimens exhibiting staining of more than 10% of invasive tumor cells considered as positive), patient age, ECOG performance status, sites of active disease (visceral versus soft tissue only), number of sites with active disease, recurrence-free interval (i.e. time form initial diagnosis of breast cancer and occurrence of distant metastases), and number of previous chemotherapeutic regimens for metastatic disease were entered as potential confounders. In analogy, multiple Cox regression models were used to identify the properties of the predictors mentioned above on progression-free and overall survival. Confounders without significant influences were removed by the backward selection method based on the Wald statistic. For all analyses, $p \leq 5\%$ was considered statistically significant. The SPSS statistical software system (SPSS, Chicago, IL, version 10.0) was used for all calculations.

Results

Univariate analyses

As shown in Table 1, clinical characteristics were equally distributed between patients treated with single-agent trastuzumab and those additionally receiving chemotherapy. Overall, 13 CRs (all observed in patients receiving trastuzumab plus cytotoxic treatment) and 23 PRs (single agent: 1, combination: 22) were observed for an objective response rate of 31% (single agent: 7%, combination: 35%, $p = 0.060$). SD was achieved in six (43%) patients treated with single-agent trastuzumab and 32 (32%) patients additionally receiving chemotherapy. Thus, the rate of clinical benefit (CR, PR or SD > 6 months) was 66% (67 of 101) in the combined treatment and 50% (seven of 14) in the single-agent trastuzumab group ($p = 0.540$). Median (95% CI) progression-free survival was 4.2 (1.77–6.63) months in patients receiving single-agent trastuzumab and 6.2 (4.45–7.95) months in patients additionally receiving chemotherapy (log-rank $p = 0.560$). Likewise, overall survival was similar between patients treated with trastuzumab alone (median 23.1 months, 95% CI 16.2–30.0) months and those patients receiving the combined treatment (median 27.0, 95% CI 19.9–34.0, log-rank $p = 0.809$). Survival curves for progression-free and overall survival according to treatment are depicted in Figure 1.

Multivariate analyses

In multivariate logistic regression analysis [entering grade of Her-2/*neu* overexpression, estrogen and progesterone receptor status, age, performance status, sites of active disease (visceral versus soft tissue only), number of sites with active disease, recurrence-free interval, and number of previous chemotherapeutic regimens for metastatic disease as potential confounders] type of treatment was the only variate showing a trend to influence the occurrence of an objective response: treatment with single-agent trastuzumab resulted in a relative risk (RR) for response of 0.154 (95% CI 0.019–1.239, $p = 0.079$). In contrast, multivariate analysis revealed no significant predictors of clinical benefit; the RR (95% CI) for clinical benefit in patients receiving single-agent trastuzumab was 0.494 (0.192–2.220, $p = 0.652$).

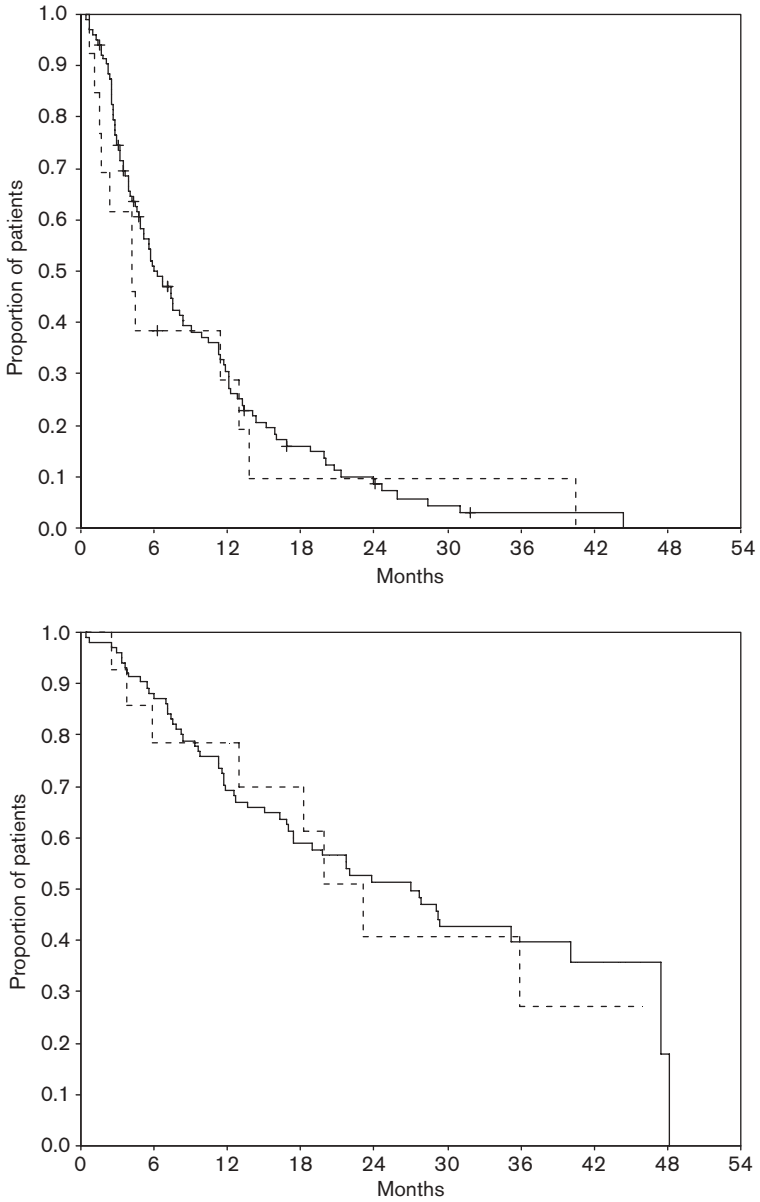
In multivariate Cox regression analysis, the number of sites of active disease was the only significant predictor of progression-free survival (RR for progression corresponding to each additional site of metastatic disease 2.156, 95% CI 1.400–3.320, $p < 0.0001$). The number of previous chemotherapeutic regimens showed a trend towards an increase in the risk of disease progression (RR 1.338, 95% CI 0.992–1.803, $p = 0.056$), whereas treatment with single-agent trastuzumab was not significantly associated with an increased risk of disease progression (RR 1.382, 95% CI 0.743–2.573, $p = 0.207$).

Grade of Her-2/*neu* overexpression (RR for grade 3+ 0.264, 95% CI 0.131–0.533, $p < 0.001$) and the number of sites with active disease (RR 3.124, 95% CI 1.829–5.338, $p < 0.001$) were the only significant predictors of overall survival, whereas treatment with single agent trastuzumab was not associated with inferior overall survival (RR 1.223, 95% CI 0.548–2.729, $p = 0.623$).

Discussion

Like many agents, trastuzumab has shown moderate efficacy in terms of response rates when used as single agent, both in chemonaive and pretreated patients with Her-2/*neu* overexpressing metastatic breast cancer [3–5]. The widespread acceptance of this agent has been based upon its low toxicity not overlapping with cytotoxic treatment, and the successful translation of the preclinically observed synergisms of trastuzumab and a series of cytotoxic agents [20,21]. Most importantly, the addition of this single agent to conventional chemotherapy has resulted in prolonged survival [6]. The enthusiasm caused by the observed response rates has often neglected the significantly enhanced toxicity occurring with the addition of other chemotherapeutical drugs to trastuzumab, which is mostly attributable to the cytotoxic agents used. In addition, there are no data suggesting that the increased response rates observed with the combined modality treatment as compared with the use of trastuzumab as a single-agent effectively translates into a clinical benefit. In fact, cross-trial comparisons between the pivotal single-agent and combination therapy studies have suggested the outcome of both treatment modalities in terms of overall or progression-free survival may not be dissimilar (C. Vogel, pers. commun.) [11]. Randomized comparative trials between trastuzumab with and without chemotherapy, however, are lacking to date. In the present retrospective study, we have addressed this issue and report on a trend towards increased response rates in

Fig. 1



Progression-free (above) and overall survival (below) curves according to type of treatment. Dotted line: single-agent trastuzumab; solid line: trastuzumab plus chemotherapy.

patients receiving trastuzumab plus chemotherapy, but this did not necessarily result in a clinical benefit in terms of progression-free or overall survival. In our patient cohort, response rates, rates of disease stabilization, progression-free survival and overall survival were comparable to those reported in previously published studies [3–6]. However, despite the similarities in baseline patients' characteristics between those receiving trastuzumab alone and those additionally receiving chemotherapy, the validity of our results may be limited by the low number of patients receiving single-agent treatment. The finding that only a minority of patients was assigned to single-agent treatment was most likely caused by treating physicians' enthusiasm caused by the high response rates reported on the combined treatment and the fear of possibly jeopardizing disease control when using trastuzumab as single agent. To exclude the possibility of selection bias of this retrospective analysis, we have carefully attempted to compare the two patient groups with respect to multiple histopathologic and clinical characteristics in multivariate analysis: although not statistically significant because of small numbers, there

were trends for those treated with single-agent trastuzumab to more likely have hormone receptor-positive disease and not to have visceral metastases. However, patients treated with single-agent trastuzumab also tended to have more sites of active disease, the latter being the strongest adverse predictor of progression-free and overall survival in our patient population.

We conclude, therefore, that prospective randomized trials should be done comparing trastuzumab alone with its combined use with chemotherapy. These studies should not only focus upon efficacy endpoints, but additionally take toxicity and quality of life endpoints into account.

Acknowledgments

The authors gratefully acknowledge the assistance of the Nurses of the Clinical Division of Oncology, Department of Internal Medicine I, University Hospital of Vienna. In addition, we would like to thank Dr Charles Vogel for fruitful discussions, Dr Ernst Rücklinger for statistical analyses, and Drs Angelika Eiper and Johann Blasina for logistic support.

References

1 Pegram M, Slamon D. Biological rationale for HER2/*neu* (c-erbB2) as a target for monoclonal antibody therapy. *Semin Oncol* 2000; **27**:13–19.
2 Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science* 1987; **235**:177–182.
3 Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, *et al.* Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002; **20**:719–726.
4 Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, *et al.* Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999; **17**:2639–2648.
5 Baselga J, Tripathy D, Mendelsohn J, Baughman S, Benz CC, Dantis L, *et al.* Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/*neu*-overexpressing metastatic breast cancer. *J Clin Oncol* 1996; **14**:737–744.
6 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344**:783–792.
7 Pegram MD, Lipton A, Hayes DF, Weber BL, Baselga JM, Tripathy D, *et al.* Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/*neu* monoclonal antibody plus cisplatin in patients with HER2/*neu*-overexpressing metastatic breast cancer refractory to chemotherapy treatment. *J Clin Oncol* 1998; **16**:2659–2671.
8 Burstein HJ, Kuter I, Campos SM, Gelman RS, Tribou L, Parker LM, *et al.* Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001; **19**:2722–2730.
9 Burris 3rd HA. Docetaxel (Taxotere) plus trastuzumab (Herceptin) in breast cancer. *Semin Oncol* 2001; **28**:38–44.
10 Miller KD, Sisk J, Ansari R, Gize G, Nattam S, Pennington K, *et al.* Gemcitabine, paclitaxel, and trastuzumab in metastatic breast cancer. *Oncology (Huntingt)* 2001; **15**:38–40.
11 Vogel CL, Franco SX. Clinical experience with trastuzumab (herceptin). *Breast J* 2003; **9**:452–462.
12 Brodowicz T, Kandioler D, Tomek S, Ludwig C, Rudas M, Kunstfeld R, *et al.* Anti-Her-2/*neu* antibody induces apoptosis in Her-2/*neu* overexpressing breast cancer cells independently from p53 status. *Br J Cancer* 2001; **85**:1764–1770.
13 Seidman AD, Fornier MN, Esteva FJ, Tan L, Kaptain S, Bach A, *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001; **19**:2587–2595.
14 Burstein HJ, Harris LN, Marcom PK, Lambert-Falls R, Havlin K, Overmoyer B, *et al.* Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. *J Clin Oncol* 2003; **21**:2889–2895.
15 Longo F, Mansueto G. Breast Cancer Conference. Trastuzumab and Capecitabine in the Treatment of Advanced Breast Cancer. Milano, 6–7 June 2002. *Tumori* 2002; **88**:A1–A10.
16 Kostler WJ, Steger GG, Soleiman A, Schwab B, Singer CF, Tomek S, *et al.* Monitoring of serum Her-2/*neu* predicts histopathological response to neoadjuvant trastuzumab-based therapy for breast cancer. *Anticancer Res* 2004; **24**:1127–1130.
17 Hudelist G, Kostler WJ, Attems J, Czerwenka K, Muller R, Manavi M, *et al.* Her-2/*neu*-triggered intracellular tyrosine kinase activation: *in vivo* relevance of ligand-independent activation mechanisms and impact upon the efficacy of trastuzumab-based treatment. *Br J Cancer* 2003; **89**:983–991.
18 Kostler WJ, Schwab B, Singer CF, Neumann R, Rucklinger E, Brodowicz T, *et al.* Monitoring of serum Her-2/*neu* predicts response and progression-free survival to trastuzumab-based treatment in patients with metastatic breast cancer. *Clin Cancer Res* 2004; **10**:1618–1624.
19 Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. *Invest New Drugs* 1992; **10**:239–253.
20 Pegram MD, Lopez A, Konecny G, Slamon DJ. Trastuzumab and chemotherapeutics: drug interactions and synergies. *Semin Oncol* 2000; **27**:21–15; discussion 92–100.
21 Pegram MD, Finn RS, Arzoo K, Beryt M, Pietras RJ, Slamon DJ. The effect of HER-2/*neu* overexpression on chemotherapeutic drug sensitivity in human breast and ovarian cancer cells. *Oncogene* 1997; **15**:537–547.