PERGAMON

European Journal of Cancer 36 (2000) 1755–1761

European Journal of Cancer

www.ejconline.com

HER2: a 'predictive factor' ready to use in the daily management of breast cancer patients?

M.J. Piccart *, A. Di Leo, A. Hamilton

Institut Jules Bordet, Unite de Chimiotherapie, Rue Héger Bordet 1, B-1000 Brussels, Belgium

Received 8 November 1999; received in revised form 20 March 2000; accepted 7 June 2000

Abstract

The past few years have witnessed an exponential increase in studies trying to identify molecular markers in patients with breast tumours that might predict for the success or failure of hormonal therapy or chemotherapy. HER2, a tyrosine kinase membrane receptor of the epidermal growth factor receptor family, has been the most widely studied marker in this respect. This paper attempts to critically review to what extent HER2 may improve 'treatment individualisation' for the breast cancer patient. © 2000 Published by Elsevier Science Ltd.

Keywords: Breast cancer; HER2/receptor tyrosine kinase; Chemotherapy; Hormonal therapy; Prediction of response

1. Introduction

Oncologists can no longer ignore the HER2 status of a patient's breast tumour: today this information has direct implications for optimal patient management in the same way hormone receptor measurements have been, and still are, impacting on treatment selection for the breast cancer patient.

The purpose of this review is neither to address the prognosis value of this tyrosine kinase membrane receptor nor to summarise the efficacy data of herceptin, the monoclonal antibody targeting HER2. Instead, the focus will be on the putative predictive value of HER2 in selecting classical forms of breast cancer therapy.

To this end, a review of the current evidence with regard to the predictive value of HER2 for hormonal therapy and chemotherapy will be carried out using published studies involving a minimum of 100 patients and moving, in each case, from the advanced disease setting to the adjuvant setting. The potential relevance of HER2 for the management of *in situ* breast cancer or for selecting candidates for herceptin therapy will not be addressed.

2. HER2: a predictive marker for hormonal therapy?

Four studies of advanced disease have investigated the relationship between HER2 expression and the outcome of second- or first-line hormonal therapy for advanced metastatic breast cancer [1–4]. Two studies [1,2] found HER2 to be associated with decreased response rates and either decreased response duration or shortened time-to-progression, whilst the other two [3,4] failed to disclose such a relationship (Table 1).

In the adjuvant setting, two prospective clinical trials, designed to look at the value of 2 years of tamoxifen versus observation or 5 years of tamoxifen versus 2 years of tamoxifen with follow-up of 14 and 8 years, respectively, were retrospectively analysed for the correlation between HER2 status and outcome [5,6] (Table 2). Of note, tumour material could only be obtained in a subset of the clinical trial population. HER2+ patients were found to fare worse on tamoxifen than on observation in the study by Blanco and colleagues [5], and did not appear to benefit from prolonged tamoxifen treatment, in contrast to HER2− patients, in the study published by Stål and co-workers [6].

In the two other adjuvant studies with reasonable length follow-ups, therapy with tamoxifen was allocated rather than randomised [7,8]. The first larger trial suggests similar benefits from tamoxifen treatment for HER2+ or HER2− patients [7], while the second, using

* Corresponding author. Tel.: +32-2-541-3206; fax: +32-2-538-0858.

E-mail address: mpiccart@ulb.ac.be (M.J. Piccart).

0959-8049/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0959-8049(00)00162-3

Table 1
HER2: a predictive factor for hormonal therapy (HT)? Advanced breast cancer

Disease setting	Author [Ref.]	No. of patients	Outcome of HER2⊕ patients versus HER2− patients			
			Response rates (%) HER2+	HER2−	*P* value	Other endpoints
Second-line HT	Leitzel [1]	300	21	41	0.004	↓ response duration and survival for HER2⊕
First-line HT	Houston [2]	241	38	56	0.02	↓ TTP for HER2⊕
	Elledge [3]	205	54	57	NS	↓ or same TTF
	Archer [4]	92	29	43	NS	Same TTP

HT, hormonal therapy; NS, non significant; TTP, time to progression; TTF, time to treatment failure.

different techniques for HER2 evaluation, applied to the progesterone-positive subset, again points to a worse outcome for HER2+ patients in general, and particularly when receiving tamoxifen [8] (Table 2).

There are several limitations to the published studies we have just reviewed. HER2 testing has always been a retrospective exercise, performed with different assays, usually on a subset of patients belonging to a clinical trial in which allocation to endocrine therapy was not always done through randomisation. The heterogeneity of the study populations is best exemplified by the wide variation in the time-to-progression (TTP) of the HER2− subset in the advanced disease trials: this TTP ranged from 7 to 11 months.

Fig. 1 summarises the current status of HER2 as a putative predictive marker for hormonal therapy.

In advanced breast cancer, 838 patients treated with hormonal therapy have been evaluated for HER2, 505 in prospective clinical trials.

With two studies showing a worse outcome for HER2+ patients and two studies failing to do so, no firm conclusions can be drawn. However, the striking observation across all studies of first-line endocrine therapy is a short TTP of less than 6 months for the HER2+ subset.

In the adjuvant setting, 1752 patients have been evaluated for HER2; 764 were enrolled in prospective trials looking at the potential benefit of 2 or 5 years of tamoxifen. No benefit emerged for HER2+ patients in three studies, while the fourth found a benefit similar to the one encountered in the HER2− subset. Again, no firm conclusions can be drawn in view of the limitations of these retrospective studies, but the potential detrimental effect of tamoxifen in HER2+ patients suggested by two of these studies is of particular concern.

3. HER2: a predictive marker for chemotherapy?

Of four studies in advanced disease which have investigated the relationship between HER2 expression and outcome of anthracycline or taxane-based chemotherapy, and which could retrieve between 35% and

Table 2
HER2: a predictive factor for hormonal therapy? Adjuvant setting

Author [Ref.]	Clinical trial treatment arms	Median follow-up (years)	No. of patients Total/HER2 test done/HER2⊕	HER-2 assay	RR of relapse	
					HER 2+ (95% confidence interval, where available)	HER2−
Blanco [5]	Randomisation 2/3 ER+	14	433/245/63	IHC		
	↗ TAM 2 year				1.22	0.80
	↘ No TAM				0.86	1.21
Stål [6]	Randomisation	8	1662/519/?	Southern blot + IHC	–	–
	↗ TAM 2 year				3.0 (0.6–15)	0.64 (0.43–1.06)
	↘ TAM 5 year					
Muss [7] (all ER+)	No randomisation Tam 5 year or not	9	1572/741/186	IHC polyclonal Ab or MAb	+T = 74% −T = 59%	+T = 73% −T = 58%
Borg [8]	No randomisation Tam 1–2 year or not	5	583/216/28	Southern + Western blot	+T = 34% −T = 54%	+T = 73% −T = 66%

ER, oestrogen receptor; IHC, immunohistochemistry; MAb, monoclonal antibody; N, node; RR, relative risk; T or Tam, tamoxifen; +T, proportion disease-free with tamoxifen treatment; −T, proportion disease-free (no tamoxifen treatment).

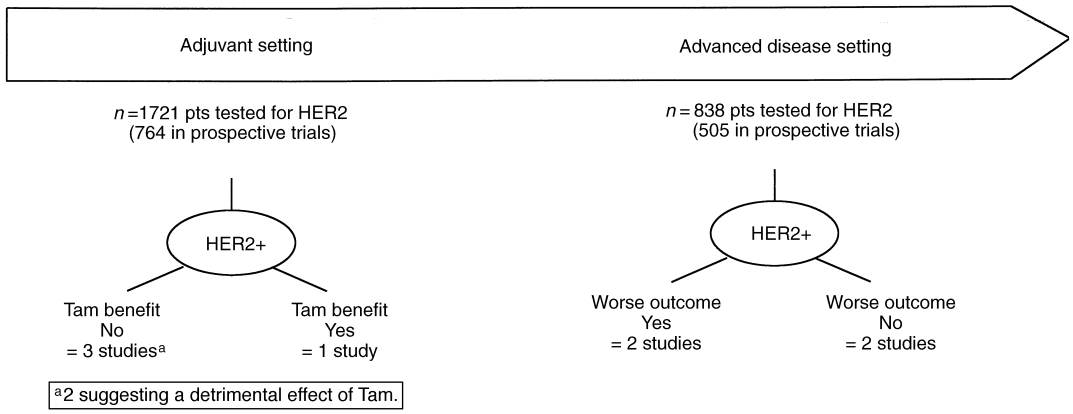

Fig. 1. HER2: a predictive factor for hormonal therapy? Conclusions.

60% of the patients' tumour blocks [9–12], only one found a differential response rate between HER2+ and HER2− patients, with the former subgroup displaying an apparently higher sensitivity to taxanes than the latter [12] (Table 3).

Of the four studies, only one [11] formally investigated the predictive value of HER2, because two different treatments (doxorubicin and paclitaxel) were compared in the two populations of HER2+ and HER2− patients. In the three other trials, the prognostic rather than the predictive value of HER2 has been evaluated, because all patients received the same chemotherapy regimen. Hence, additional studies are needed to fully evaluate the worth of HER2 as a predictive marker in advanced disease.

The claimed predictive value of HER2, as far as chemotherapy is concerned, is derived mainly from studies performed in the adjuvant setting.

Three rumours are circulating and, rightly or wrongly, are influencing clinical practice.

- "HER2⊕ predicts for resistance to adjuvant cyclophosphamide, methotrexate, 5-fluorouracil (CMF)."
- "HER2⊕ predicts for sensitivity to "adequately dosed" anthracycline (A)-based chemotherapy."
- "HER2⊕ patients benefit more from A- than CMF-based regimens."

Is there really 'strong' evidence to support these statements?

3.1. Statement 1: HER2+ predicts resistance to adjuvant CMF

Three research groups, who have prospectively compared, in node-positive or node-negative patients, various CMF regimens to either one perioperative cycle or to observation, have met with variable success rates, ranging between 16 and 87%, in retrieving the patients' tumour blocks for HER2 evaluation through different immunohistochemistry techniques [13–15] (Table 4). Two groups found CMF to benefit only the HER2− subset [13,14], while in the Milan trial with a 20-year median follow-up, both HER2+ and HER2− patients had a decreased risk of relapse and death when treated with CMF [15].

Table 3
HER2: a predictive factor for chemotherapy? Studies in advanced disease

Disease setting	Author [Ref.]	Chemotherapy	No. of pts tested	% of trial population	Outcome of HER2⊕ pts versus HER2⊖ pts		
					Response rates (%)		*P* value
					HER2+	HER2−	
LABC	Rozan [9]	FAC	167	52	31	20	NS
Metastatic	Niskanen [10]	FEC	103	60	39	34	NS
	Hamilton [11]	A	92	35	39	41	NS
		or					
		T	87		24	24	NS
	Baselga [12]	T	122	58	65	35	0.002

A, doxorubicin; C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; LABC, locally advanced breast cancer; NS, non significant; T, paclitaxel.

Table 4
HER2 and CMF-based adjuvant chemotherapy

Author [Ref] (follow-up)	Population/% tested for HER2 (HER2 assay)	Treatment arms	N total/HER2+ (%)	Disease-free survival ↙ HER2+		↘ HER2−	*P* value
Gusterson [13] (6 years)	Node-positive 61 IHC (MAb)	CMFP peri	255/55 (22)	29%	NS	36%	0.0001
		CMFP post ± peri	491/85 (17)	38%		52%	
Allred [14] (5 years)	Node-negative 16 IHC (poly Ab)	Nil (low risk)	307/40 (13)	≃76%	NS	≃82%	0.0003
		Nil	146/35 (24)	≃70%		≃60%	
		CMFP	160/40 (25)	≃78%		≃80%	
Ménard [15] (20 years)	Node-positive 87 IHC (MAb)	Nil	155/25 (16)				
		CMF	180/29 (16)	HR = 0.48+		HR = 0.64+	

C, cyclophosphamide; F, 5-fluorouracil; HR, hazard ratio; IHC, immunohistochemistry; M, methotrexate; MAb, monoclonal antibody; P, prednisone; Poly Ab, polyclonal antibody; post; postoperative; peri, perioperative; NS, non-significant; +, where no treatment is the reference group.

3.2. Statement 2: HER2+ predicts sensitivity to anthracycline adjuvant therapy

In terms of disease-free survival, one cycle of perioperative FAC chemotherapy appeared to benefit exclusively the HER2− subset in the European Organization for the Research and Treatment of Cancer (EORTC) trial, which is clearly limited by the small size of the HER2+ group (60 patients in total) [16] (Table 5). In the larger Cancer and Leukemia Group B (CALGB) trial, the benefit of adequate cyclophosphamide, doxorubicin, 5-fluorouracil (CAF) doses in comparison to suboptimal CAF doses appeared to be larger in the HER2+ subset, but can not be ruled out in the HER2− subset [17] (Table 5). In the Southwest Oncology Group (SWOG) biological correlative study of HER2 expression as a predictor of outcome in a trial comparing adjuvant CAF+tamoxifen with tamoxifen alone, there was a suggestion, but no statistical certainty, that the addition of CAF chemotherapy was more effective in HER2+ than in HER2− patients [18] (Table 5).

3.3. Statement 3: HER2+ patients benefit more from adjuvant anthracycline (A) than non A-based adjuvant chemotherapy

Three adjuvant studies provide a direct and prospective comparison between such regimens: melphalan–doxorubicin–5-fluorouracil (5-FU) versus melphalan–5-FU [19], doxorubicin, cyclophosphamide (AC) versus CMF [20] and epirubicin, cyclophosphamide (EC) versus CMF [21] (Table 6). The retrieval of tumour blocks was particularly remarkable in the first study, with a success rate of 94% [19]. Using an interaction test, a clear trend in favour of A-based regimens in HER2+ patients was seen in the three studies, reaching

Table 5
HER2 and anthracycline-based adjuvant chemotherapy

Author/ Group [Ref] (follow-up)	Population/% tested for HER2 (HER2 assay)	Treatment arms	*n* total/HER2+ (%)	Disease-free survival ↙ HER2+		↘ HER2−	*P* value
Clahsen EORTC [16] (4 years)	Node−, premen 65 IHC (MAb)	Nil	210/31 (15)	77%	NS	78%	0.05
		FAC perioperative	230/29 (13)	90%		85%	
Thor CALGB [17] (9 years)	Node+ 63 IHC (MAb)	low dose CAF	322/88 (27)	50%	0.001	60%	0.058
		standard dose CAF	670/184 (27)	71%		65%	
Ravdin SWOG [18] (4 years)	Node+, postmen 40 IHC (MAb)	Tam	132/17 (13)	56%	0.07	82%	NS
		CAF+Tam	463/76 (16)	75%		84%	

A, doxorubicin; C, cyclophosphamide; F, 5-fluorouracil; IHC, immunohistochemistry; MAb, monoclonal antibody; poly Ab, polyclonal antibody; premen, premenopausal; postmen, postmenopausal; Tam, tamoxifen; NS, non significant.

Table 6
HER2 and anthracycline (A) versus non A-based adjuvant chemotherapy

Author/Group [Ref.] (follow-up)	Population/% tested for HER2 (HER2 assay)	Treatment arms	*n*	Risk ratio A versus non-A regimens	*P* value	*P* interaction test
Paik NSABP-B11 [19] (13 years)	Node +, ER− 94	PAF or	HER2⊕ = 239	0.60	0.001	0.02
	IHC (cocktail)	PF	HER2⊖ = 399	0.96	0.74	
Paik NSABP-B15 [20] (?)	Node+ ?	AC or	HER2⊕ = 404	0.83	0.13	0.14
	IHC (cocktail)	CMF	HER2⊖ = 951	1.04	0.65	
Di Leo Belgian [21] (4 years)	Node+, ER± 60					
	A) IHC (MAb)	EC or CMF	HER2⊕ = 37	0.33	0.08	0.10
			HER2⊖ = 255	1.16	0.56	
	B) IHC (cocktail)	EC or CMF	HER2⊕ = 61	1.06	0.90	0.84
			HER2⊖ = 232	0.99	0.97	

A, doxorubicin; C, cyclophosphamide; E, epirubicin; ER, oestrogen receptor; F, 5-fluorouracil; IHC, immunohistochemistry; M, methotrexate; MAb, monoclonal antibody; P, melphalan.

significance in the first trial only. Disappointingly, when the Belgian investigators moved to the cocktail technique used by the NSABP with the hope of improving their results, they completely lost the trend favouring the epirubicin-based regimen! Once again, the limitations of the published studies relate to their retrospective nature, the variability in the HER2 assays used and in the chosen criteria for positivity.

Fig. 2 summarises the current status of HER2 as a putative predictive molecular marker for chemotherapy. In the adjuvant setting, 6007 patients, all belonging to prospective trials, have been evaluated for HER2. When focusing on HER2+ patients, it can be seen that approximately 93 contributed to the combined chemo-hormonal therapy versus hormonal therapy alone question, 309 contributed to the CMF question, 332 to the A optimal dose question and 704 to the A versus non-A question. These are clearly small populations, which do not allow statistical stability to be reached. The data are controversial for CMF; they suggest benefit from adequately dosed A regimens and perhaps some higher benefit with A regimens relative to non-A combinations.

4. Methodological limitations of the studies so far reported

All the studies discussed in this review are retrospective companion studies to clinical trials, most of which were multicentric. For this reason, they have two

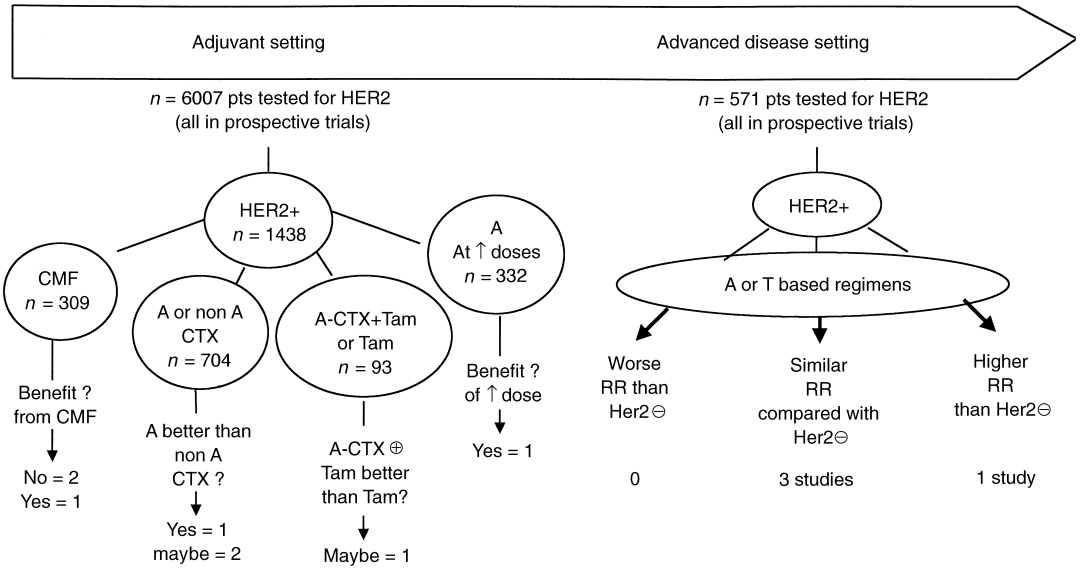

Fig. 2. HER2: a predictive factor for chemotherapy? Conclusions from studies performed so far. A, doxorubicin; C, cyclophosphamide; CTX, chemotherapy; F, 5-fluorouracil; M, methotrexate; RR, response rate; Tam, tamoxifen, A or non A CTX, anthracycline or non-anthracycline-based chemotherapy; T, taxanes.

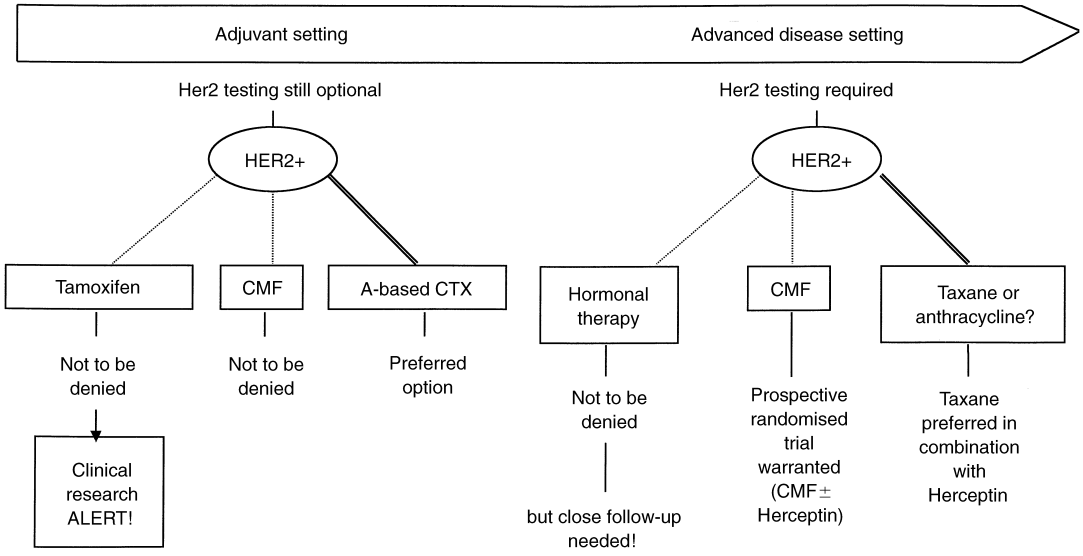

Fig. 3. Use of HER2 as a 'predictive' factor: proposed guidelines for clinical practice. A, anthracycline; C, cyclophosphamide; M, methotrexate; F, 5-fluorouracil; CTX, chemotherapy.

important methodological limitations, related to the marker assays and to the statistical analysis employed.

Archived samples came from different pathology centres and were fixed according to different procedures, which may impact on the results of immunohistochemistry, the most 'popular' HER2 evaluation method so far. In addition, as no international standards yet exist for HER2 immunohistochemistry testing, the definition of marker positivity or negativity are defined individually by each study, and interobserver variation in reporting tumour marker status may limit the reproducibility of any study results. For this reason, it would be worthwhile to evaluate gene amplification (by fresh *in-situ* hybridisation), in addition to protein overexpression, given that nucleic acids are more stable over time than proteins. So far, no data regarding this issue have been presented on a series of archived samples from a multicentric study.

The interpretation of the current predictive studies is also severely limited by a number of statistical issues:

- Firstly, many of the studies presented are relatively small and lack statistical power in the subgroup analyses that are required to assess the 'predictive value' of HER2.
- Secondly, the relatively low prevalence of HER2 positivity further reduces the power of these studies, which seek to demonstrate a statistically significant difference in outcome between treatment arms in marker-positive patients and a non-significant difference in the marker-negative group.
- Thirdly, as tissue samples were available from only a subset of the patients belonging to the clinical trial, there is considerable room for statistical bias in the reported results.

5. Conclusions

Based on the known activity of Herceptin±chemotherapy in HER2+ patients [22,23] and on this review, which emphasises the lack of 'level 1' evidence-based studies that convincingly demonstrate the value of HER2 as a predictive marker for resistance or sensitivity to classical forms of breast cancer therapy as well as their methodological limitations, we propose the following provisional guidelines for the management of HER2+ patients in clinical practice (Fig. 3). Clearly these guidelines are likely to change in the near future, as more data are being generated.

In the advanced disease setting, HER2 testing is now required given that herceptin, the anti-HER2 monoclonal antibody, is registered for use in Europe (since May 2000). These HER2+ patients should not be denied hormonal therapy, but should be closely followed; ideally, they should be evaluated prospectively in a trial comparing CMF±Herceptin, and they are candidates for therapy with taxane+Herceptin combinations or Herceptin alone.

In the adjuvant setting, routine HER2 testing cannot be presently advocated. However, it is useful information in 'high-risk' patients for the future, given their likelihood of a relapse, and it is required for the potential inclusion of the patient into adjuvant clinical trials exploring the value of Herceptin, which are currently being initiated. HER2+ patients should not be denied tamoxifen; they should be preferentially treated with A-based chemotherapy; patients with contraindications to anthracyclines should not be denied CMF. The Tamoxifen data in the adjuvant setting are extremely worrisome and represent 'a clinical research alert' for clinical research cooperative groups.

References

1. Leitzel K, Teramoto Y, Konrad K, *et al*. Elevated serum c-erbB-2 antigen levels and decreased response to hormone therapy of breast cancer. *J Clin Oncol* 1995, **13**, 1129–1135.
2. Houston SJ, Plunkett TA, Barnes DM, Smith P, Rubens RD, Miles DW. Overexpression of c-erbB2 is an independent marker of resistance to endocrine therapy in advanced breast cancer. *Br J Cancer* 1999, **79**, 1220–1226.
3. Elledge RM, Green S, Ciocca D, *et al*. HER-2 expression and response to tamoxifen in estrogen receptor-positive breast cancer: A Southwest Oncology Group Study. *Clin Cancer Res* 1998, **4**, 7–12.
4. Archer SG, Eliopoulos A, Spandidos D, *et al*. Expression of ras p21, p53 and c-erbB-2 in advanced breast cancer and response to first line hormonal therapy. *Br J Cancer* 1995, **72**, 1259–1266.
5. Blanco AR, De Laurentils M, Carlomagno C, *et al*. 20 year update of the Naples gun trial of adjuvant breast cancer therapy: evidence of interaction between c-erbB2 expression and Tamoxifen efficacy. *Proc Am Soc Clin Oncol* 1998, **17**, (abstract 373), 97a.
6. Stål O, Fernö M, Borg A, Nordenskjöld B, and the South and South-East Sweden Breast Cancer Groups. ERBB2 expression and benefit from 5 versus 2 years of adjuvant tamoxifen for postmenopausal stage II breast cancer patients. *Proc Breast Cancer Res Treat* 1997, **46** (abstract 112), 32.
7. Muss H, Berry D, Thor A, *et al*. Lack of interaction of tamoxifen (T) use and ErbB-2/HER/Neu (H) expression in CALGB 8541: a randomized adjuvant trial of three different doses of cyclophosphamide, doxorubicin and fluorouracil (CAF) in node-positive primary breast cancer (BC). *Proc Am Soc Clin Oncol* 1998, **18** (abstract 256), 68a.
8. Borg A, Baldetorp B, Fernö M, *et al*. ERBB2 amplification is associated with tamoxifen resistance in steroid-receptor positive breast cancer. *Cancer Lett* 1994, **81**, 137–144.
9. Rozan S, Vincent-Salomon A, Zafrani B, *et al*. No significant predictive value of c-erbB-2 or p53 expression regarding sensitivity to primary chemotherapy or radiotherapy in breast cancer. *Int J Cancer (Pred Oncol)* 1998, **79**, 27–33.
10. Niskanen E, Blomqvist C, Franssila K, Hietanen P, Wasenius VM. Predictive value of c-erbB-2, p53, cathepsin-D and histology of the primary tumour in metastatic breast cancer. *Br J Cancer* 1997, **76**, 917–922.
11. Hamilton A, Larsimont D, Paridaens R, *et al*. A study of the value of p53, c-erbB2 and Bcl-2 in the prediction of response to doxorubicin and Taxol® as single agents in metastatic breast cancer; a companion study to EORTC 10923. *Clin Breast Cancer* 2000, in press
12. Baselga J, Seidman AD, Rosen PP, Norton L. HER2 overexpression and paclitaxel sensitivity in breast cancer: therapeutic implications. *Oncology* 1997, **11**(3 Suppl. 2), 43–48.
13. Gusterson BA, Gelber RD, Goldhirsch A, *et al*. Prognostic importance of c-erbB-2 expression in breast cancer. *J Clin Oncol* 1992, **10**, 1049–1056.
14. Allred DC, Clark GM, Tandon AK, *et al*. HER-2/neu in node-negative breast cancer: prognostic significance of overexpression influenced by the presence of in situ carcinoma. *J Clin Oncol* 1992, **10**, 599–605.
15. Ménard S, Valagussa P, Pilotti S, *et al*. Benefit of CMF treatment in lymph node-positive breast cancer overexpression HER2. *Proc Am Soc Clin Oncol* 1999, **18** (abstract 257), 9a.
16. Clahsen PC, van de Velde CJH, Duval C, *et al*. P53 protein accumulation and response to adjuvant chemotherapy in premenopausal women with node-negative early breast cancer. *J Clin Oncol* 1998, **16**, 470–479.
17. Thor AD, Berry DA, Budman DR, *et al*. ErbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. *J Natl Cancer Inst* 1998, **90**, 1346–1360.
18. Ravdin PM, Green S, Albain KS, *et al*. For SWOG, NCCTG, NCI-Canada, ECOG and CALGB. Initial report of the SWOG biological correlative study of c-erbB-2 expression as a predictor of outcome in a trial comparing adjuvant CAF T with tamoxifen (T) alone. *Proc Am Soc Clin Oncol* 1998, **17** (abstract 374), 97a.
19. Paik S, Bryant J, Park C, *et al*. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. *J Natl Cancer Inst* 1998, **90**, 1361–1370.
20. Paik S, Bryant J, Park C, *et al*. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive hormone receptor-negative breast cancer. *J Natl Cancer Inst* 1998, **90**, 1361–1370.
21. Di Leo A, Larsimont D, Beauduin M, *et al*. CMF of anthracycline-based adjuvant chemotherapy for node-positive breast cancer patients: 4 year results of a Belgian randomised clinical trial with predictive markers analysis. *Proc Am Soc Clin Oncol* 1999, **18** (abstract 258), 69a.
22. Cobleigh MA, Vogel CL, Tripathy D, *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.
23. Norton L, Slamon D, Leyland-Jones B, *et al*. Overall survival (OS) advantage to simultaneous chemotherapy (CRx) plus the humanized anti-HER2 monoclonal antibody herceptin (H) in HER2 overexpressing (HER2+) metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 1999, **18** (abstract 483), 127a.