HER-2 as a Target for Breast Cancer Therapy

Michail Ignatiadis, Christine Desmedt, Christos Sotiriou, Evandro de Azambuja, and Martine Piccart

The human epidermal growth factor tyrosine kinase receptor 2 (HER-2/*neu*, c-erbB2) was initially discovered in 1985 by two independent laboratories (refs. 1, 2; Fig. 1). The merit for building the first bridge between this laboratory discovery and the clinic goes to Denis Slamon. In an initial series of 189 primary breast tumors, he reported HER-2 gene amplification in 30% of them and showed that it was a significant predictor of both overall survival and time to relapse in these patients (3). Currently, it is estimated that the HER-2 gene is amplified in ∼20% of breast cancers (4).

HER-2 belongs to a family of cell surface tyrosine kinase receptors, the ErbB or epidermal growth factor receptor family with four members: epidermal growth factor receptor (ErbB1 or HER-1), ErbB2 (HER-2), ErbB3 (HER-3), and ErbB4 (HER-4; ref. 5). Apart from their importance in normal human physiology, these receptors have been implicated in the development of many human cancers. In tumorigenesis, ErbB receptors are activated by mechanisms such as gene mutation, gene amplification, and abnormal production of epidermal growth factor family ligands. Ligand binding to HER-1, HER-3, and HER-4 receptors causes the formation of receptor homodimers or heterodimers and the activation of the tyrosine kinase domain, which eventually leads to the activation of intracellular signaling pathways. Although HER-2 has no ligand identified, HER-2 exists in a constitutively extended open conformation, making it the preferred heterodimerization partner of the other ErbB family members.

HER-2 plays an essential role in normal cardiac development (6), and HER-2 gene amplification has been identified as an important event in the oncogenesis of a subset of human breast cancers (5). Aberrant HER-2 activation increases cell proliferation, resistance to apoptosis, angiogenesis, invasive growth, and metastatic behavior through the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin and the mitogen-activated protein kinase pathways. Following the demonstration of a key role of HER-2 in the biological behavior of a subset of breast cancers, two major types of HER-2 inhibitors have been developed for clinical use: humanized antibodies, which are directed against the extracellular domain of the receptor, and small-molecule tyrosine kinase inhibitors, which compete with ATP in the tyrosine kinase domain of the receptor.

Trastuzumab (Herceptin) is the first recombinant humanized monoclonal antibody directed at the extracellular domain of the HER-2 protein. As a result of preclinical laboratory studies showing synergy or additivity between trastuzumab and several cytotoxic agents (7), a seminal phase III clinical trial (8) was designed in which trastuzumab added to anthracycline- or taxane-based chemotherapy was compared with the same chemotherapy drugs given without trastuzumab; a longer time to disease progression, a higher rate of objective response, and a remarkable reduction in the risk of death were shown for patients with HER-2-positive metastatic breast cancer (MBC) offered trastuzumab upfront (9). The most important adverse event was cardiac dysfunction, but it occurred predominantly in women receiving concurrent anthracycline.

Because a survival benefit is rarely seen in randomized clinical trials for MBC, clinicians realized the great potential of trastuzumab, if used sooner, for improving cure rates of women with HER-2-positive breast cancer. This enthusiasm led to the conduct of four major multicentered trials [Herceptin Adjuvant (HERA), Breast Cancer International Research Group 006 (BCIRG 006), National Surgical Adjuvant Breast and Bowel Project (NSABP B-31), and North Central Cancer Treatment Group 9831 (NCCTG N9831)] and two smaller clinical trials [Finnish Herceptin (FINHER) and Protocole Adjuvant dans le cancer du sein 04 (PACS 04)] of trastuzumab in the adjuvant setting (refs. 10–16; Table 1). More than 14,000 women were randomized between chemotherapy alone and trastuzumab plus chemotherapy. The trials differed in the percentage of patients with node-negative disease, type of chemotherapy used, timing of trastuzumab initiation, and schedule and duration of trastuzumab administration (17). In all these trials, with the exception of Protocole Adjuvant dans le cancer du sein 04, trastuzumab reduced the risk of recurrence by 40% to 50% and the risk of death by one-third (Table 1).

There are still many unanswered questions, however, that are going to require further translational research efforts. One major question concerns the role of anthracycline-containing versus non-anthracycline-containing regimens in HER-2-positive disease. The non-anthracycline docetaxel/carboplatin/trastuzumab regimen, which was used in the BCIRG 006 trial, is preferred if significant and/or multiple cardiac risk factors are present or if there is a higher risk of an early relapse. True predictive biomarkers of docetaxel/carboplatin/trastuzumab, however, are currently lacking. Another important question is whether to favor a strategy of administering trastuzumab sequentially or concurrently with adjuvant chemotherapy. An unplanned analysis of sequential and concurrent of N9831 showed a significant benefit in disease-free survival and a nonsignificant benefit in overall survival favoring concurrent over sequential taxane plus trastuzumab treatment (18). These results should be interpreted with caution because they are derived from an unplanned analysis. A third unanswered question pertains to the optimal duration of trastuzumab, which has been empirically chosen as 1 year. The HERA trial results of 2 years versus 1 year of trastuzumab are eagerly awaited. Other trials investigating this question are the Protocol
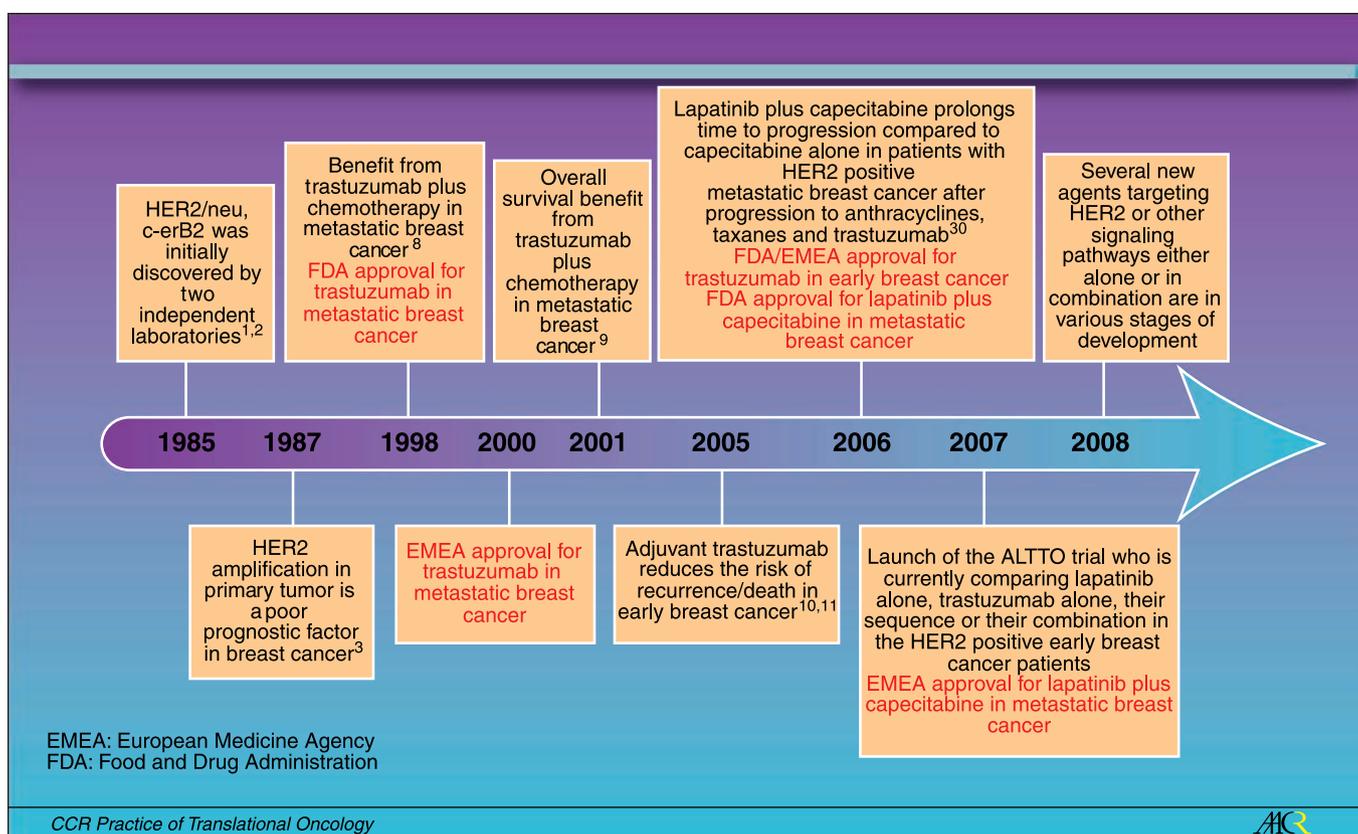
Fig. 1. HER-2 as a target therapy for breast cancer: from bench to bedside.

of Herceptin Adjuvant with Reduced Exposure (PHARE), a randomized comparison of 6 versus 12 months in all women receiving Adjuvant Herceptin trial comparing 1 year versus 6 months of trastuzumab, and the Short-or-Long Duration (SOLD) trial looking at 1 year versus 9 weeks of trastuzumab. Yet another area of investigation focuses on the study of the prevalence and risk factors of trastuzumab-related cardiac toxicity. Despite the stringent inclusion criteria and the close cardiac monitoring, trastuzumab was still related with cardiac toxicity in the adjuvant trials (Table 2; refs 14–16, 19–21). In contrast to anthracycline-related cardiotoxicity, however, trastuzumab-induced cardiac toxicity does not seem to increase with cumulative dose; moreover, it is not associated with ultrastructural changes in the myocardium and is generally reversible (21).

The ''success story'' of trastuzumab (Fig. 1) has been attributed to the identification of a subset of breast cancer tumors (HER-2-positive) that show (*a*) dependency on the target to which the therapy is directed and (*b*) existence of a predictive biomarker (HER-2-positive status of the primary tumor) for benefit from trastuzumab. Nevertheless, there is still much to be learned in terms of predictive biomarkers for benefit from trastuzumab. Indeed, even the definition of what constitutes a HER-2-positive tumor has recently evolved (4). Intriguingly, Paik et al. have suggested that the benefit of trastuzumab may extend beyond women with HER-2-positive breast cancer as it is currently defined (22). Furthermore, although it has been shown that tumors with extra copies of

HER-2 as a result of polysomy 17 are different from those with extra copies resulting from gene amplification, it is not clear that the former tumors would benefit from existing HER-2-targeted therapies (23). Recently, Korkaya et al. have proposed that the effect of HER-2 amplification on mammary carcinogenesis, tumorigenesis, and invasion may be due to its effect on tumor initiating cells with stem cell-like properties (24). Therefore, these investigators suggest that the clinical efficacy of trastuzumab may relate to its ability to target the tumor initiating cell population in HER-2-amplified tumors. Further supporting this hypothesis, Li et al. have shown that neo-adjuvant chemotherapy increased the percentage of tumor-initiating cells, whereas lapatinib, a small-molecule tyrosine kinase inhibitor of HER-2 (and HER-1), produced a nonstatistically significant decrease in the percentage of these cells (25).

Differences in response to anti-HER-2 agents such as trastuzumab may be also explained through the study of the host and minimal residual disease. IgG polymorphisms have been recently shown to predict clinical efficacy of trastuzumab-based therapy in a small group of patients with HER-2-positive MBC (26). The presence of minimal residual disease in women with HER-2-positive early breast cancer (27) could potentially be another factor explaining and/or modulating response and resistance to trastuzumab (28).

Trastuzumab, however, can only cure a subgroup of patients with HER-2-positive early breast cancer and cannot cure patients with HER-2-positive MBC. The ambitious aim is to identify treatment strategies that will cure patients with

Table 1. Efficacy results in the adjuvant trastuzumab trials

	Regimen	Median follow-up (y)	Patients enrolled	Disease-free survival, HR (95% CI)	Overall survival, HR (95% CI)	Reference
HERA	Chemo→observation	2	1,698			(13)
	Chemo→H × 1 y		1,703	0.63 (0.53-0.75), $P < 0.0001$*	0.63 (0.45-0.87), $P = 0.0051$*	
	Chemo→H × 2 y		1,701	NR	NR	
NCCTG 9831	AC→P→observation		819			(12)
	AC→P→H	2.9	981			
	AC→PH		814	0.48 (0.41-0.57), $P < 0.0001$*	0.65 (0.51-0.84), $P = 0.0007$	
NSABP 31	AC→P→observation		1,024			
	AC→PH		1,019			
BCIRG 006	AC→T→observation	3	1,072			(14)
	AC→TH		1,076	0.61 (0.48-0.76), $P < 0.0001$	0.59 (0.42-0.85), $P = 0.004$	
	TCH		1,074	0.67 (0.54-0.83), $P = 0.00003$	0.66 (0.47-0.93), $P = 0.017$	
FINHER	V→FEC or T→FEC	3	116			(13)
	VH→FEC or TH→FEC		116	0.42 (0.21-0.83), $P = 0.01$†	0.41 (0.16-1.08), $P = 0.07$	
PACS 04	FEC or ET→observation	4	268			(16)
	FEC→H or ET→H		260	0.86 (0.61-1.22), $P = 0.41$†	1.27 (0.68-2.38)	

Abbreviations: Chemo, chemotherapy; H, trastuzumab; AC, doxorubicin/cyclophosphamide; P, paclitaxel; PH, paclitaxel/trastuzumab; T, docetaxel; TH, docetaxel/trastuzumab; TCH, docetaxel/carboplatin/trastuzumab; VH, vinorelbine/trastuzumab; FEC, 5-fluoruracil/epirubicin/cyclophosphamide; V, vinorelbine; ET, epirubicin/docetaxel; HR, hazard ratio; 95% CI, 95% confidence interval; NR, not reported.
*Censored population.
† Recurrence-free survival.

HER-2-positive disease while ensuring minimal toxicity for each individual patient. With this in mind, we need to identify relevant predictive biomarkers and treatment strategies to avoid, delay, or overcome trastuzumab resistance. Novel agents targeting HER-2 and other members of the ErbB family of receptors, or targeting downstream signaling components of the ErbB [PI3K/AKT/mammalian target of rapamycin (mTOR), Ras/Raf/MEK/extracellular signal-regulated kinase] or different pathways [insulin-like growth factor-I receptor (IGFIR), estrogen receptor (ER), and angiogenesis pathway], have been developed and are undergoing evaluation in women with HER-2–positive breast cancer.

Pertuzumab is a humanized monoclonal antibody directed at an epitope within the HER-2 dimerization domain that disrupts dimerization between ErbB2 and other ErbB receptors. Encouraging results from a phase II study of the combination of trastuzumab and pertuzumab in MBC patients previously exposed to trastuzumab (29) led to the initiation of a phase III registration study in the first-line setting.

Beyond monoclonal antibodies, small-molecule tyrosine kinase inhibitors have also been developed, lapatinib (Tykerb), a tyrosine kinase inhibitor of ErbB1 and ErbB2, being the most advanced in clinical development (17). The combination of lapatinib plus capecitabine produced a longer time to progression than capecitabine alone in patients with HER-2–positive locally advanced breast cancer or MBC whose cancer progressed after anthracyclines, taxanes, and trastuzumab (30). These results led to regulatory approval for

Table 2. Cardiac safety results in the adjuvant trastuzumab trials

	Regimen	Median follow-up (y)	Class III/IV congestive heart failure (% of patients)	Systolic dysfunction (% of patients)	Reference
HERA	Chemo→observation	2	0	0.5	(19)
	Chemo→H × 1 y		0.6	3	
	Chemo→H × 2 y		NR	NR	
NCCTG 9831	AC→P→observation	3	0.3	4-5.1	(20, 21)
	AC→P→H		2.8	4-7.8	
	AC→PH		3.3	5.8-10.4	
	AC→P→observation		0.9	NR	
	AC→PH		3.8	15.9	
BCIRG 006	AC→T→observation	5	0.5	10	(14)
	AC→TH		1.9	18	
	TCH		0.4	8.6	
FINHER	V→FEC or T→FEC	3	NR	6	(13)
	VH→FEC or TH→FEC		0	3.5	
PACS 04	FEC or ET→observation	4	0.4	2.2	(16)
	FEC→H or ET→H		1.7	4.2	

lapatinib by the European Medicine Agency and the Food and Drug Administration. In this trial, it was also observed that fewer patients in the lapatinib arm developed central nervous system metastases, although this difference was not statistically significant. Because of these promising results of lapatinib in MBC, this drug is currently being tested in the neoadjuvant and adjuvant settings. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial, which has an extensive translational research component, is currently comparing lapatinib alone, trastuzumab alone, their sequence, or their combination in the HER-2-positive early breast cancer patients.

Beyond agents targeting the cell surface ErbB receptors, others targeting downstream signaling pathways have been developed. Activation of the PI3K pathway, either through phosphatase and tensin homologue loss or through PI3K mutations, has been implicated as a major determinant of trastuzumab resistance (31, 32). However, Paik et al. found no correlation between phosphatase and tensin homologue (PTEN) loss and relapse-free survival in the NSABP 31 patient cohort (33). Several inhibitors of the PI3K pathway such as PI3K, AKT, and mammalian target of rapamycin are currently under development, with the mammalian target of rapamycin inhibitors at a more advanced stage of clinical development. Insulin-like growth factor-I receptor pathway is also thought to play a role in trastuzumab resistance (34).

Two other approaches to improve outcome of HER-2–positive patients cotarget HER-2 signaling and either angiogenesis or estrogen receptor signaling. The combination of trastuzumab with the humanized monoclonal anti-vascular endothelial growth factor (VEGF) antibody bevacizumab was active as first-line treatment in women with HER-2–positive MBC (35) and this combination is currently being tested in a phase III trial. Because there is a cross-talk between the ER and ErbB1/ErbB2 pathways, combining ER and HER2 inhibitors was shown to have clinical benefit for patients with ER-positive/HER-2–positive breast tumors (36).

Another approach for the treatment of HER-2-positive breast cancer is the inhibition of heat shock protein 90 (17-allylamino-17-demethoxygeldanamycin), a chaperone protein that helps with the proper expression and folding of its client proteins. The combination of 17-allylamino-17-demethoxygeldanamycin and trastuzumab has shown preliminary efficacy in HER-2–positive MBC patients (37).

The growing list of new targeted agents poses many challenges with respect to our ability to evaluate them effectively and rapidly in HER-2-positive disease. One way to move forward would be to develop an international collaboration in which a multi-arm clinical trial could test many potential combinations of the new agents in the metastatic setting. The objective would be to ''kill'' the suboptimal combinations early on to focus on the most promising ones and move them into the adjuvant setting. However, concern has been raised that heavily pretreated MBC patients do not provide the optimal population to test new agents. Therefore, it has been proposed that the new agents should be moved as early as possible to neoadjuvant trials. These would incorporate biological-only ''therapeutic windows'' and extensive translational research to identify both early readouts of clinical benefit and novel biomarkers to then be tested in the adjuvant setting. This approach is exemplified by the Neoadjuvant and Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) and ALTTO trials. The next generation of adjuvant trials should not only be able to choose the best arm from among those tested but also be powered to address more relevant biomarker questions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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